Addition of the Emetic Agent PP796 to Paraquat Products

Jon Heylings

Dermal Technology Laboratory Ltd
Keele, United Kingdom

THE QUEEN'S AWARDS FOR ENTERPRISE: INTERNATIONAL TRADE 2016

Why has the Emetic concentration in PQ products re-surfaced now?

- Department of Health project won by DTL (2018-2020) to assess the skin decontamination of Methyl Salicylate (hydrophobic) and Paraquat (hydrophilic) poisons
- Review of the toxicity of the chemicals, lethal dose in man, oral vs skin exposure and prevention measures currently in force
- Collaboration with PHE, DSTL at Porton Down and Technical Review Group of Poisons Experts
- DTL acquired radiolabelled PQ and is studying the absorption from various formulations
- Reviewed the current status of PQ Registrations in 2018 and FAO Specifications for the Technical Concentrate and Gramoxone

FAO Specification

- Paraquat concentrates must contain the triazolopyrimidine compound PP796, as stipulated by the FAO for agricultural pesticides
- Important that it is included at an appropriate concentration in order to be effective in human poisoning cases
- The FAO specification as required by EPA/PMRA stipulates that "*emesis must occur in about half an hour in at least 50% of cases*"
- For the US TK (320g/L) the PP796 concentration must be at least 0.8g/L. This is equivalent to 0.5g/L (or 0.05%) in standard Gramoxone which contains 200g/L paraquat ion
- The ratio of 400 : 1 (PQ ion : emetic) is based on an estimation of the effective dose of PP796 in man by Rose (CTL/R/390R) in 1976
- This was ratified by the Agrochemicals Board and published
- Surprisingly this has not changed since it was pointed out that the emetic was ineffective in animals and human poisoning surveys back in 1990

RESEARCH REPORT

REPORT NO: CTL/R/390 (R)

THE CONCENTRATION OF PP 796 REQUIRED TO PRODUCE EMESIS IN EXPERIMENTAL ANIMALS AND AN ESTIMATION OF THE EMETIC DOSE IN MAN

IMPERIAL CHEMICAL INDUSTRIES LIMITED
CENTRAL TOXICOLOGY LABORATORY
ALDERLEY PARK, MACCLESFIELD, CHESHIRE

TABLE 1

The emetic action of PP 796

	Dose	Nos. Vomiting	% Vomiting response	Total dose (mg)
Dog*	0.5 mg/kg	3/8	35	
	1.5 mg/kg	6/8	75	
Pig**	0.25 mg/kg	0/8	0	
	0.5 mg/kg	3/8	35	
	1.0 mg/kg	5/8	63	
Monkey+	0.1 mg/kg	4/19	21	
	0.2 mg/kg	6/16	38	
	0.5 mg/kg	4/5	80	
Man++	0.015 mg/kg	0/2	0	1
	0.03 mg/kg	4/37	11	2
	0.06 mg/kg	1/2	50	4
	0.11 mg/kg	1/1	100	8

* Data from Farrell (1970) Vol. II.
** Data from Broome (1972)
\+ Data from Davies and Hepworth (1969)
++ Data from Bayliss (1973)

Emetic Action of PP796 in Man

Data from Table 1 (CTL/R/390)

mg	mg/kg	n	Nos vomiting	% vomiting response
1	0.015	2	0	0
2	0.03	37	4	11
4	0.06	2	1	50
8	0.11	1	1	100

Complete Data from Clinical Report PH20992

mg	mg/kg	n	Nos vomiting	% vomiting response
0.25	0.0035	1	0	0
0.5	0.007	1	0	0
1	0.015	2	0	0
2	0.03	3	0	0
3	0.04	2	0	0
4	0.06	2	1 (at 30min)	50
8	0.11	1	1 (at 2hr)	100

PH2079/2C

Possible side effects

These are shown below:-

No.	Dose (mg.)	Possible side effects
1	0.25	Nil.
2	0.5	Mild nausea and light headedness.
3	1.0	Nausea at 1 hour.
4	1.0	Severe dizziness at 15 minutes. Felt as if he had taken "pep pills" from 1 - 4 hours.
5	2.0	Mild nausea.
6	2.0	Nil.
7	2.0	Dizziness and sweating at 30 minutes followed by some nausea.
8	3.0	Dizziness and nausea marked ½ - 2 hours.
9	3.0	At 30 minutes dizzy, pale, sweating. Nausea marked.
10	4.0	Nausea and flushing at 15 minutes. Vomited at 30 minutes. Light headedness for 2 - 3 hours.
11	4.0	Dizziness, flushing of face, sweating from ½ - 2 hours.
12	6.0	At 30 minutes sweaty, flushed and light headed. Vomited at 2 hours.

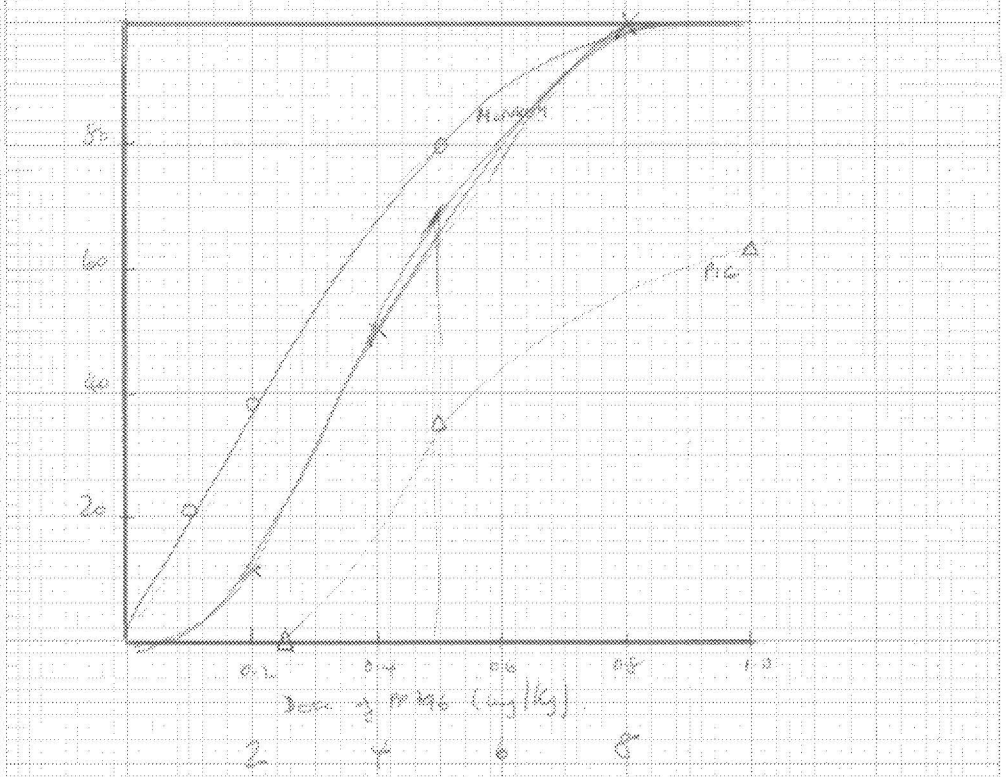
CONCLUSIONS

No clearly defined results emerged from this study, although certain suggestive ones were seen. The following points may be made:-

(1) The half life of ICI 63,197 in the human, following a single oral dose is between 1½ and 3½ hours.

(2) No clear effect was seen on pulse rate, although a slight fall was seen in some subjects. Similarly, no clear effect was seen on blood pressure, although in some subjects a fall was seen in the 2 - 4 hour period.

Mike Rose's Lab Book with a hand drawn graph of the human dose response to PP796, fitting the Pharms volunteer data between the primate and pig CTL data.



Mike Rose's lab book annotation to generate the 11% incidence of emesis in man at the 2mg dose

Emetic Action of PP796

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Monkeys*	0.1mg/kg	4/19	21	
	0.2mg/kg	6/16	38	
	0.5mg/kg	4/5	80	
Man	0.03mg/kg	1/~~9~~	~~[illegible]~~ 11	2
	0.06mg/kg	1/2	50	4
	0.11mg/kg	1/1	100	8

1) Human / animals
2) Acceptable ... buccal absorption
3) Human studied based on tablet formulation - not aqueous
4) Intravenous infusion (dog) indicates rate of increase is important
5) Emesis clearly ... [illegible]
6) Actual ~~[illegible]~~ dose likely to be much higher.

* Single monkeys given multiple challenges

Clinical Trials with ICI 63197 (Bayliss 1973 PH 20992B)

All Trials used a dose of 2mg ICI 63197 (PP796).

Trialist	Centre	Disease	Nos Patients or Volunteers	Nos of Dosings to each person	Vomiting Incidences	
Crooks	Dundee	Normal Vol	3V	1	0/3	-
Davies	Manchester	Endocrinology	8V	1	1/8	at 45M
Davies	Manchester	Glucose Tol	2V	1	0/2	-
Kerr	Glasgow	Asthma	4P	1	1/4	no time quoted
Palmer	Aberdeen	Asthma	4P	1	1/4	no time quoted
Beumer	Utrecht	Emphysema	12P	1	0/12	-
Eccleston	Edinburgh	Depression	4P	63	0/252	21 day study TDS
Magnus	Birmingham	Schizophrenia	6P	21	0/126	7 day study TDS
Magnus	Birmingham	Anxiety	5P	21	1/105	Vomited once then settled 7 day study TDS
Zacharias	Bebington	Hypertension	3P	112	0/336	28 day study QDS
Davies	Manchester	Obesity	4P	126	0/504	6 week study TDS
		TOTALS	55			

% incidence by dosing
4/1356 or 0.3%

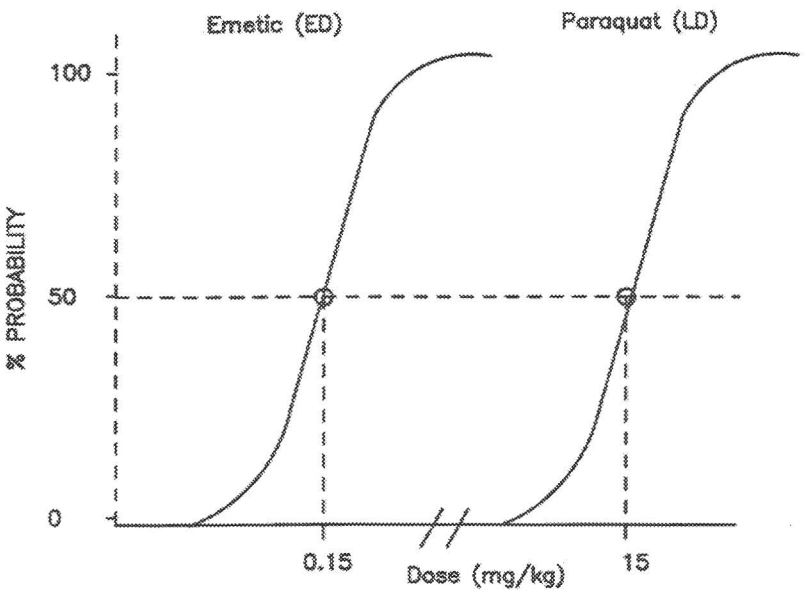
% incidence of individuals
4/55 or 7%
(but disease may predispose or exacerbate nausea/vomiting)

The 4/37 (or 11% value) is based on 4 volunteers vomiting at 2mg but not taking into account that they didn't vomit on the subsequent occasions they were given this dose. There was no emesis at 2mg in either of the 2 Normal volunteer studies. This should be 4/1356, not 4/37 in any case

The ED dose response for the emetic and the LD curve for PQ are both quite steep. Unique position of having both in multiple species including man.

Bringing these together by either diluting the product or raising the emetic to an effective level in the current product is likely to provide a significant improvement in survival in both accidental and suicidal poisoning.

PARAQUAT TO EMETIC RATIO



Dog data suggests the above ratio for effective emesis following a lethal paraquat dose.

ie $\frac{\text{PARAQUAT}}{\text{EMETIC}} = \frac{15}{0.15} = 100$

GRAMOXONE (1977) $\frac{\text{PARAQUAT}}{\text{EMETIC}} = \frac{20}{0.05} = 400$

GRAMOXONE (1990) X5 EMETIC = 0.25% RATIO $= \frac{20}{0.25} = 80$

or

GRAMOXONE L X 2.5 EMETIC = 0.12% RATIO $\frac{10}{0.12} = 83$

Safer Formulation Strategy

- No disagreement that a higher emetic concentration in paraquat products should be evaluated
- Magnoxone delivered the PSAC requirements. It contained 5X emetic built and higher gel built into a 200g/L product
- Cost constraints of circa £30m /annum plus a new emetic plant forced a reduction to 3X emetic (1.5g/L) and lower gelling capacity that were finally used in Inteon
- Improvement in survival was demonstrated in Sri Lanka and was in line with expectations
- A new Inteon with 2.5 g/L emetic would further improve survival but questions would be raised on the selection of the original concentration of 0.5g/L

EPA United States Environmental Protection Agency

Paraquat Dichloride: One Sip Can Kill

en español

On this page:

The Accidental Poisoning Problem

The California Poison Control System and the Central California Children's Hospital reviewed data from 1998-2009 and identified more than 1,400 cases of accidental poisonings caused by storage of non-food substances in soda bottles, unmarked bottles, cups or glasses. Several of the deaths involved the accidental ingestion of pesticides, including paraquat. [1]

Recent Deaths from the Accidental Ingestion of Paraquat

The California Poison Control System and the American Association of Poison Control Centers (AAPCC) recently sent letters of concern to EPA regarding a series of deaths from accidental ingestion of the pesticide paraquat in the San

Recent publication from EPA shows that there are still a significant number of accidental poisonings in children.
If an effective emetic concentration had been present in the product that met the FAO specifications and regulatory requirements then these children may well have survived!