

Addition of the Emetic Agent PP796 to Paraquat Products

**Extracts from a presentation given to Syngenta
Product Safety, Jealotts Hill, UK
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ICI Central Toxicology Laboratory Report CTL/R/390(R) 1977. Author : Dr Mike Rose

- Report CTL/R/390(R) contains summary data from various animal and human studies on the paraquat emetic agent, PP796, conducted by Syngenta's former organisation ICI, in the 1970s. This includes dose responses to cause vomiting in dog, pig, monkey and man, following various oral doses of the emetic agent in each species and a prediction of the effective dose of emetic that would cause vomiting within 1 hour in man.
- The report Author concluded that the emetic was **10 X more potent** in man compared with the 3 other vomiting animal species and estimated a concentration that should be added to the paraquat concentrate, Gramoxone, so if a child ingested a minimally lethal volume of the herbicide(10ml) then they would have a greater than 50% chance of vomiting within one hour.
- This concentration 0.5g/L PP796 in a 200g/L paraquat product was endorsed by the Board of ICI Agrochemicals in 1977 and has been added to the 200g/L Gramoxone SL paraquat product concentrate, or at an equivalent percentage of the paraquat content (0.8g/L in the USA product Gramoxone Max) ever since.

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

ICI Central Toxicology Laboratory
Research Report issued in 1977
Author : Dr Mike Rose

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

TABLE 1

The emetic action of PP 796

	<u>Dose</u>	<u>Nos. Vomiting</u>	<u>% Vomiting response</u>	<u>Total dose (mg)</u>
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)

ICI Pharmaceuticals data on the emesis side-effect of the phosphodiesterase drug in man

- In the human volunteer trial PH20992 with the phosphodiesterase drug, that later became the emetic PP796 used in paraquat products, it was noted that one of the two volunteers vomited at 30 min following a dose of 4mg, and the single volunteer given 8mg vomited at 2 hours. There was no vomiting at the five other doses of 0.25, 0.5, 1, 2 or 3 mg in the human volunteers in the study.
- By deleting and replacing various doses in the volunteer study, a plausible human dose response curve to the emetic of 0, 11, 50 and 100% was presented in report CTL/R/390(R) to make it appear that the emetic was **10 X more potent** in man compared to 3 other vomiting species. This is not the same as the actual human data in the same study conducted by ICI Pharmaceuticals .
- The complete data from ICI Pharmaceuticals has 3 additional dose levels, including 3mg where there was no vomiting. A zero incidence of vomiting at 2mg that had been replaced with a 4/37 (11%) response, which should have been 4/1356 since the 2mg was given multiple times. Also, the single volunteer who vomited at 8mg was well beyond the time criteria set by the Author to save lives.

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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

Syngenta failed to notify the Regulatory Authorities or correct the FAO Specification

- Surveys survival rate following paraquat poisoning were conducted in the UK and Asia in the 1980s, following the addition of the emetic. Unsurprisingly, none of these hospital surveys showed any improvement in survival following the registration of the new version of Gramoxone with emetic in 1977. Any vomiting at high doses was too late to prevent death since paraquat reaches peak blood levels within one hour.
- This fabrication of the human dose response with the emetic was pointed out to Company management back in 1990 and again in 1995, when the product was being re-registered in Europe. On each occasions the Company failed to notify the Regulators or deal with this matter of what is an effective emetic dose in man.
- In the early 2000s, Syngenta ran a poisoning survey with a small 3X higher emetic (Gramoxone Inteon). This demonstrated an improvement in survival with the emetic level at a threshold dose in man with improved survival at low ingestion volumes of paraquat. However, Syngenta remain highly defensive that the original emetic level was effective and have failed to pursue an even higher emetic strategy.
- In 2018, this matter was raised again. Syngenta claim they were unaware of the actions of their former managers and now trying to defend their actions. There have been numerous poisonings with paraquat since these mistakes were made.

The “One Sip Can Kill” publication from the California Poison Control System shows that there are still a significant number of accidental poisonings in the USA in children since as little as 10ml of Gramoxone can be lethal.

If an effective emetic concentration to cause prompt emesis in man had been present in the product and at a level which is much higher than stated in the FAO specification, then these children may well have survived.

The extensive knowledge of the pharmacology of the emetic and the toxicology of paraquat in man strongly suggests a combination of dilution of the product and higher emetic would save many lives.

An official website of the United States government.

Due to a lapse in appropriations, EPA websites will not be regularly updated. In the event of an environmental emergency imminently threatening the safety of human life or where necessary to protect certain property, the EPA website will be updated with appropriate information. Please note that all information on the EPA website may not be up to date, and transactions and inquiries submitted to the EPA website may not be processed or responded to until appropriations are enacted.

We've made some changes to EPA.gov. If the information you are looking for is not here, you may be able to find it on the EPA Web Archive or the January 19, 2017 Web Snapshot.

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Paraquat Dichloride: One Sip Can Kill

[en español](#)



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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