IMPERIAL CHEMICAL INDUSTRIES

PLANT PROTECTION DIVISION
Fernhurst Haslemere Surrey
England

RIC4203

SUMMARY DATA SHEET

PP796

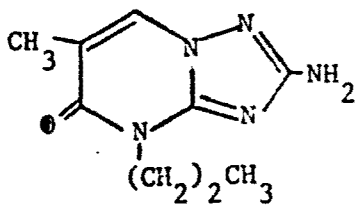
1. IDENTITY

1.1 CHEMICAL NAME AND FORMULA

1.1.1 Systematic name : 2-amino-4,5-dihydro-6-methyl-4-propyl-s-triazolo (1,5-a) pyrimidin-5-one. This conforms to IUPAC nomenclature.

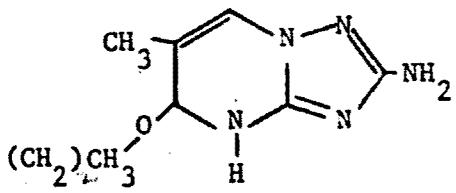
1.1.2 Empirical formula : $C_9 H_{13} N_5 O_1$

1.1.3 Structural formula :



1.1.4 Molecular weight : 207.2

1.1.5 Technical material : Technical PP796 is greater than 90% pure. The main impurity is the 5-oxypropyl derivative :



This compound is coded ICI 69,631

1.2 OTHER NAMES

PP796 was previously known as R50,796 and, before that, as ICI 63,197.

2. PHYSICAL AND CHEMICAL PROPERTIES

2.1 PHYSICAL PROPERTIES

PP 796 is a white to cream crystalline powder, melting at 163-165°C and with negligible vapour pressure.

It is without smell.

PP 796 has a solubility of 2 g/litre in water, 83 g/litre in chloroform and 6 g/litre in 95% ethanol.

2.2 STABILITY

PP 796 has proved physically and chemically stable at room temperature (27°C) for seven years.

2.3 COMPATIBILITY

PP796 is compatible with and stable in aqueous solutions of paraquat, eg. 'Gramoxone'.

3. METHODS OF ANALYSIS

3.1 FORMULATION ANALYSIS

A portion of samples is diluted and the PP796 extracted into chloroform. This extract is then evaporated to dryness. For formulations containing surfactant, the residue is washed onto a Florisil column with n-hexane and the n-hexane eluant discarded. PP796 is eluted from the Florisil column using dichloromethane which is then removed by evaporation. The residue is made up to a known volume with chloroform.

An aliquot is injected into a gas chromatograph equipped with flame ionisation detection, and the peak area for PP796 is measured by electronic integrator. The PP 796 content of the sample is determined by standard comparison.

The method has been satisfactorily applied to 'Gramoxone' in which the PP796 content is 0.05% w/v.

3.2 RESIDUE ANALYSIS

A method for the determination of PP796 in crop tissues, soil and water is being developed.

4. APPLICATION

4.1 TYPE OF PESTS CONTROLLED

PP 796 is not a pesticide. It is to be introduced as an adjuvant in the herbicidal liquid 'Gramoxone' for the express purpose of inducing vomiting in those people who, accidently or deliberately, ingest the weedkiller.

4.2 CROPS ON WHICH THE PRODUCT WILL BE USED

All those crops, and non-crop situations, for which 'Gramoxone' is currently cleared and recommended.

4.3 FORMULATIONS FOR INTENDED USE

It is intended to add PP796 to 'Gramoxone' at the rate of 500 mg/litre. The product will thus consist of :

		% w/v	
Paraquat (as dichloride)		'x'	
Surfactants		5.2	Where 'x'
Pyridine Base stench		1.0	gives 200 g
PP796		0.05	paraquat/litre
Anti-foam		0.01	
Water	to	100.00	

4.4 APPLICATION, MODE OF ACTION, PHYTOTOXICITY

These will remain unchanged and will be as standard 'Gramoxone'.

5. RESIDUE DATA

Data on residues of PP796 in crops, soil and water await the development of a suitable method of analysis. Samples are being retained for this purpose.

6. EXPERIMENTAL DATA ON TOXICITY

6.1 ACUTE TOXICITY TO VERTEBRATES

6.1.1 Vertebrates other than mammals

PP796 has been screened for fish toxicity by a rapid bioassay technique using rainbow trout. The results are :

15 ppm : No effect
20 ppm : Threshold concentration for effect
30 ppm : Toxic or highly toxic

6.1.2 Mammals

The following acute LD50 values have been established :

Species	Route	LD50 (mg/kg)
Rat	Oral	150 - 155
Mouse	Oral	300 - 310
Rat (Female)	Intravenous	50 - 60
Rat (Male)	Intravenous	60 - 75
Mouse	Intravenous	> 150

In rabbits 5 mg/kg intravenously killed one out of two rabbits, 20 mg/kg killed two out of two rabbits.

The mice that died after oral administration had convulsions and died within minutes of dosing with the exception of a few animals which died from general inanition two to four days later.

Rats dosed orally showed rapid respiration immediately after administration of the compound. All the animals which died did so from general inanition within 48 hours of dosing except for one animal which died after 3 days.

Animals receiving intravenous doses developed a rapid respiration. The majority of mice receiving 100 and 150 mg/kg had convulsions within an hour after dosing but many recovered. The mice that died did so within fifteen minutes of dosing. The rats receiving an intravenous dose salivated profusely within a few minutes of dosing. All the rats which died, except for one, died within the first twenty-four hours.

No gross abnormalities were seen at autopsy.

6.1.3 Skin Irritation

PP796 0.3% cream and PP796 3.0% ointment were applied twice daily for ten consecutive days to the intact, shaved skin of six albino rabbits. Slight to moderate erythema and desquamation were observed with the cream applications and slight erythema with the ointment.

Similar applications of the cream to abraded skin caused slight to mild erythema and desquamation, while the ointment caused only slight erythema.

Neither of these preparations caused sensitisation in the rabbit.

6.1.4 Emetic Effects : Pharmacology

Pharmacologically PP796 is a phosphodiesterase inhibitor. It increases the resting levels of cyclic AMP in the guinea pig lung and kidney.

In tests with perfused isolated guinea pig lung, PP796 at a concentration of 5 µg/ml inhibited almost completely the histamine released following injection of antigen. At lower doses the effect was extremely variable. PP796 is active against bronchospasm induced by a large dose of histamine.

On this pharmacological basis the compound was investigated (as ICI 63,197) for the control of asthma in man. The human emetic response (see section 6.4) prevented further therapeutic development. The maxium tolerated non-emetic dose of PP796 in monkeys and marmosets appears to be in the range of 0.1 to 0.5 mg/kg.

6.2 CUMULATIVE TOXICITY

Two groups of rats were given PP796 by mouth in doses of 5 mg/kg and 1.5 mg/kg daily for 18 days. There were no changes attributable to the compound.

Two dogs were given daily increasing oral doses of PP796 from 0.1 mg/kg to 1.5 mg/kg over 39 days. The female vomited approximately 2½ hours after dosing at 0.5 mg/kg on the 5th day and was slightly ataxic after a dose of 0.6 mg/kg four days later. The male vomited on several occasions; after the twenty-first dose (1.3 mg/kg), the twenty-eighth dose (1.5 mg/kg) and after feeding on the 29th day. No histological changes were observed in either of the animals.

Three groups of rats were fed 0.25, 1.25 and 5 mg PP796/kg daily for three months. At the end of the three month period five male and five female rats from the highest dosage group remained undosed for twelve weeks to assess the reversibility of any possible lesions.

No abnormalities attributable to the compound were found in the rats in the highest dosage group on haematological and histological examination.

On biochemical examination of the high dose level rats, no abnormalities were observed in the levels of SGOT, ICDH or total protein. Slightly elevated levels of alkaline phosphatase were found in both the male and female treated rats on day 21; on day 35 the levels were significantly different from controls but by day 84 had returned to the normal range. Significantly elevated levels of urea were present in female rats on day 35 and in all five tested females after 84 days. Male rats also showed a slight elevation of serum urea levels on day 35 but not on day 84. The kidneys of the treated rats were normal. There were no significant differences between organ weights in treated and control rats.

There were no histological changes attributable to PP796 in the rats left for twelve weeks.

Three groups of dogs were fed 0.15, 0.5 and 1.5 mg PP796/kg daily for 3 months. One male and one female from the top dose group remained undosed for six weeks after the dosing period to assess the reversibility of any possible lesions.

Vomiting occurred sporadically in six of the animals in the highest dose groups and three in the middle dose group from the ninth day onwards.

No abnormalities attributable to the compound were found in the dogs on haematological, biochemical and histological examination and there were no effects on blood pressure, heart and respiration rate, ECG or organ weights.

No changes attributable to PP796 were found in the dogs.

Female proven rabbits were dosed orally with 0.25, 0.75 and 1.25 mg PP796/kg on days 6-18 of pregnancy, and female rats were fed 0.25 and 1.25 mg PP796/kg on days 6-15 of pregnancy inclusive.

Both rats and rabbits dosed at 1.25 mg/kg showed signs of maternal toxicity ie. lack of appetite, poor maternal weight gain and (in rabbits) two spontaneous abortions. In rabbits, 0.75 mg/kg and 1.25 mg/kg also caused an increase in resorptions although this was not observed in rats.

In rats and rabbits PP796 has no teratogenic effects at doses used and has little significant effect on pregnancy, littering or weaning.

6.3 METABOLISM

C^{14}-labelled PP796 has been dosed orally to rat, mouse, guinea pig, beagle and rhesus monkey. The greater part of the radioactivity is excreted rapidly in the urine. A rhesus monkey vomited within 3 hours of receiving 0.08 mg/kg; the vomit contained 42% of the dose, of which at least 93% appeared to be unchanged PP796. Monkey, rat and guinea pig produce one major metabolite common to all three species. This compound, coded ICI 68,916, is the 6-hydroxymethyl derivative of PP796. It constituted 33-38% of the total ^{14}C administered to the rhesus monkey, guinea pig and dog, and 15% in the rat.

6.4 EFFECTS ON MAN

PP796, as ICI 63,197, was granted a Clinical Trials Certificate (No CSD/29/77) on 23 October 1970. This was converted to Clinical Trials Certificate of Right (No. 0029/0077) on 5 August 1974.

In clinical trials PP796 showed no consistent effect upon blood pressure of either normotensive or hypertensive subjects, no beneficial effect on body weight in obesity and no effect on thyroid, or adreno-cortical function.

The effects of dosing with PP796 were nausea, vomiting and dizziness at 1 mg unit doses and above. Angina pectoris appeared in two subjects following chronic dosing of 2 mg and above after four and six weeks respectively. The effects ceased on cessation of dosing. Capillary fragility with a positive Hess's Test was seen in one subject. The half-life of PP796 in man was between 1½ and 3½ hours.

7. REFERENCES

The above summary was prepared from full documentary evidence submitted by ICI Pharmaceuticals Division to Committee for the Safety of Drugs in support of a request for a Clinical Trial Certificate, subsequently granted (see section 6.4).

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