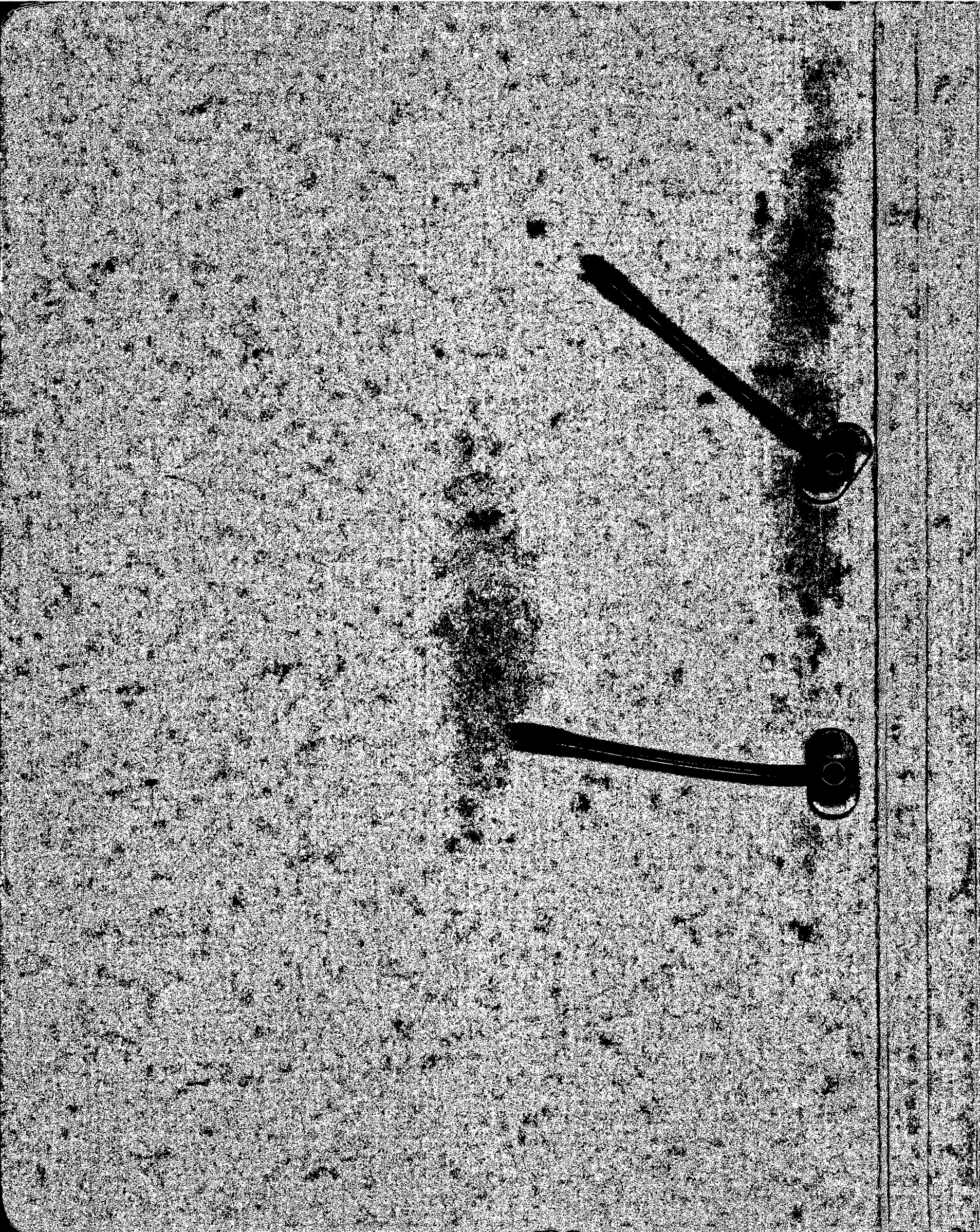


| | | | |
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| | PARQUAT: | EMETIC (1) | |
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RAILEX

Marbleboard

POLIFILE PL54



Saved on
9
Immunities +
Manufacture
Sept 02.

PP796

Formerly known as ICI 63,197 or R50796

2-amino-6-methyl-5-oxo-4-n-propyl-4,5-dihydro-5-triazolo (1,5-a) pyridine

| report no | oral | dermal | skin | eye | inhal | genotox | other |
|-----------------------------|--|--|---|-----------------|-------------------------------------|---|--|
| CTL/L/2034 10.5.88 (1,3) | Rat: MLD 100-150 mg/kg Mouse: MLD 300-310 mg/kg | | | | | | |
| (2,3) | | | | | | | IV: LD50 Female Rat 50-60 mg/kg, Male 60-75 mg/kg. Mouse >150 mg/kg. Rabbits; 5 mg/kg killed 1 of 2 animals, 20 mg/kg killed both. |
| CTL/L/2004 10.5.88 | | MLD > 2000 mg/kg | | | | | |
| CTL/T/1277 20.3.79 | | slight irritant rat skin | not a strong sensitiser (Stevens) | slight irritant | 0.49% particles in respirable range | | Daily skin applic to rats; sl skin irritant after 4 days. Signs of toxicity after 5 applications, 1 rat found dead after a total dose of 0.6 g |
| (3) | | 0.3% cream and 3% ointment x2 daily for 10 days to intact shaved skin of rabbits. Cream; SI-mod signs of irritation: ointment; slight irritation. 12 applic of 0.3% cream and 0.3% ointment were ointment to G.pigs caused mild irritation | Neither 0.3% cream or 3% ointment were sensitisers in rabbits | | | | |
| CTL/L/1839 17.12.87 | | | | | | Negative +/- S9 in TA1535,1537,1538,9 8,100 Negative to 4x strains of Sal Typhimurium | |
| (3) | | | | | | | |
| (3) | | | | | | | 18 day oral - rats. No abnormalities attributable to PP796 following oral ingestion of 1.5 or 5 mg/kg/day |

(3)

39 day oral- dogs. No histological changes following oral ingestion of increasing doses from 0.1-1.5 mg/kg over 36 days.

(1,3)

90 day dietary study in rats (0.25, 1.25 and 5 mg/kg/day). There were some minor changes in some clin chem parameters, but there were no treatment related effects on haematology, organ weights or histopath.

(1,3)

90 day feeding study in dogs (0.15, 0.5 and 1.5 mg/kg/day). Aside from sporadic vomiting, there were no treatment related effects on haem, clin chem, organ weights or histopath. No effects on BP, heart and respiration rate, ECG or organ weights.

(1,3)

(1,3)

Developmental: PP796 has no teratogenic effects and no significant effects on pregnancy, littering or weaning in rats and rabbits given daily doses of up to 1.25 mg/kg/day

(3)

Oncogenicity: A 78 week study in mice, dosed at 5 or 20 ppm (1.25 and 5 mg/kg/day), indicated that the material is not carcinogenic

Efficacy as an emetic

In addition to the above, the effect of PP796 on the toxicity of paraquat to experimental animals and the evaluation of the effectiveness of the addition of the emetic to PQ formulations on the toxicity of Pq to humans has been summarised in MII Section 3 Appendix A: The Emetic PP976 19.4.95.

(1) Scott RC Correspondence 27.5.94 citing:

Anon

Safety Evaluation Results

Pharmaceuticals Division Report No. ICI63197 1983

(2) Data cited in Scott RC correspondence file on PP796

(3) Ospenson JN

Application to F&DA

June 1977

ZENECA LTD
ZENECA AGROCHEMICALS
Fernhurst Haslemere Surrey
England

91/414/EEC
REVIEW OF PARAQUAT DICHLORIDE
UNDER REGULATION 3600/92

PARAQUAT DICHLORIDE

DOCUMENT M-II, Section 3

TOXICOLOGICAL AND METABOLISM STUDIES

APPENDIX A: THE EMETIC PP796

RAD374
ARC/EJH
19 April 1995

91/414/EEC
REVIEW OF PARAQUAT DICHLORIDE
UNDER REGULATION 3600/92

DOCUMENT M-II : SECTION 3

APPENDIX A

CONTENTS

1. RATIONALE BEHIND THE ADDITION OF AN EMETIC AGENT TO FORMULATIONS OF PARAQUAT
2. THE EMETIC PP796
3. THE EFFECT OF PP796 ON THE TOXICITY OF PARAQUAT TO EXPERIMENTAL ANIMALS
4. EVALUATION OF THE EFFECTIVENESS OF THE ADDITION OF PP796 TO PARAQUAT FORMULATIONS ON THE TOXICITY OF PARAQUAT TO HUMANS

1. **RATIONALE BEHIND THE ADDITION OF AN EMETIC AGENT TO FORMULATIONS OF PARAQUAT**

Over 30 years of practical use has demonstrated that paraquat does not present a risk to human health when handled and used according to normal agricultural practice.

Human poisonings have however occurred through oral ingestion of paraquat formulations. Efforts to reduce the incidence of poisonings and fatalities resulting from the accidental oral ingestion of paraquat formulations have been an on-going priority for ICI (now ZENECA).

Two complementary approaches have been taken towards the inclusion of formulation additives to reduce the incidence of poisoning resulting from the accidental oral ingestion of paraquat formulations. These formulation approaches are themselves complementary to additional company product stewardship initiatives which have included improvements in packaging and labelling and emphasis on farmer education and training.

The Use of Alerting Agents

The first approach was to ensure that paraquat formulations could not be mistaken for drinks suitable for human consumption. This has resulted in the addition of a distinctive smell and a colour. A stenching agent must not be too unpleasant for the legitimate user of the product but must be sufficient to clearly differentiate the product from beverages with which it might otherwise be confused. The stenching agent used in liquid paraquat formulations satisfies these requirements.

Aqueous formulations of paraquat are dark brown in the absence of a dye. The 'natural' colour of such formulations is not unlike that of certain common beverages such as tea, coffee or soft drinks. To clearly differentiate paraquat formulations from beverages a distinctive blue dye is added resulting in a blue/green liquid. Few human drinks (or foodstuffs) are blue in colour and the addition of both stench and dye together help limit any potential for confusion with drinks intended for human consumption.

The Use of a Potent Emetic

The second approach was to incorporate an emetic with the objective of inducing rapid emesis such that insufficient paraquat is retained in the gastrointestinal tract to cause poisoning following accidental oral ingestion (and secondarily, to alert the person or those in the vicinity that the product has been ingested in order to improve the likelihood of the person receiving rapid medical treatment).

The principal criteria for the selection of an appropriate (effective) emetic were as follows:

SPEED AND MODE OF ACTION

The emetic must produce a rapid vomiting response prior to the absorption of toxic amounts of paraquat. It should act centrally and should not produce its action via an irritant effect on the gastric system; irritancy could facilitate the absorption of paraquat.

SPECIFICITY

The agent must be able to act in the presence of paraquat, i.e. appropriate animal experiments must provide evidence that paraquat does not interfere with the mode or speed of action of the emetic.

HUMAN SAFETY

The emetic should be toxicologically acceptable and harmless to the user of the product in which it is incorporated.

ENVIRONMENTAL SAFETY

The emetic should not have a harmful effect on the environment.

STABILITY

The emetic must be stable in the presence of paraquat and vice versa. The emetic should not interfere with the herbicidal properties of paraquat.

An assessment was made of the following candidate emetic agents, most of which were excluded on the basis that they did not meet one or more of the necessary criteria.

Matricaria

This is the ground flower heads of the camomile plant. It is irritant in action, unreliable and, being insoluble in water, would be of no practical value for use in paraquat formulations.

Mustard

This is also highly irritant and insoluble.

Salts of heavy metals (eg. copper, antimony and zinc)

These agents have been firmly rejected by modern medical opinion because of their high toxic risk. They would also be unacceptable from an environmental perspective.

Sodium chloride

This emetic, commonly used in domestic poisoning incidents, is no longer generally recommended by the medical profession. Its efficacy is variable and a number of deaths have occurred following its use.

Apomorphine

This agent, although highly effective, can only be administered by intramuscular injection. It is unstable in air. It is therefore clearly of no practical value for inclusion in paraquat formulations.

Ipecacuanha

This agent is widely used as an orally administered emetic, it acts on the central nervous system but is also a gastric irritant. When administered in excessive amounts (approximately 10x the emetic dose) fatalities have occurred. This emetic was seriously considered by ICI for inclusion in paraquat formulations but a study in cynomolgus monkeys found that the response was unpredictable and only effective at doses associated with toxic symptoms.

2. THE EMETIC PP796**History**

PP796 is a triazolo-pyridine originally discovered by ICI Pharmaceuticals. It was extensively studied as a potential drug for the relief of asthma. Mammalian toxicology studies were completed to the satisfaction of the UK Committee for the Safety of Medicines which granted a Clinical Trials Certificate, enabling human clinical trials to take place. However during these trials it became clear that PP796 was of unexpectedly high emetic potency in humans.

(Bayliss, 1973)

It was therefore withdrawn from further development as a drug. Its emetic properties did, however, indicate considerable potential for use with paraquat formulations, and studies were therefore undertaken to establish whether PP796 could match the criteria established for a suitable emetic.

Mode of action

Following administration of an oral dose, PP796 is rapidly absorbed in mammals, peak plasma levels are observed in man within an hour of administration.

(Bayliss, 1973)

In species which vomit such as pig, dog, monkey and man (rodent species do not vomit) the rise in plasma level is associated with the onset of vomiting. This generally occurs within 15 minutes of dosing. Vomiting may be repeated four or five times within the first hour. Thereafter the effect ceases, probably as a consequence of the rapid metabolism and excretion of the compound. Evidence for the action of PP796 being centrally mediated is provided by:

- the rapid onset of vomiting and absence of irritant effects;
- the production of vomiting in dogs following intravenous administration at plasma levels similar to those producing the effect after oral administration.

(Case & Dunlop, 1977)

The proposed pharmacological rationale for the action of PP796 involves the inhibition of phosphodiesterase.

(Foulkes, 1978)

Dose required

PP796 is an extremely potent oral emetic, in a study to determine the vomiting response of cynomolgus monkeys (*Macaca fascicularis*) an oral dose of 2 mg PP796/kg bodyweight was sufficient to cause vomiting in five out of seven animals within 30 minutes of administration. The remaining two animals both vomited within approximately one hour of administration.

(Purser et al., 1978)

The emetic response of dogs to a range of single oral dose levels of PP796 (0, 0.1, 0.5, 1.0, 3.0, 10.0 or 20.0 mg/kg bodyweight) has been investigated. Emesis, with subdued behaviour, was produced at dose levels in the range 0.5 to 30 mg PP796/kg bodyweight, no effects occurred at 0.1 mg PP796/kg bodyweight. The onset of vomiting and the duration and severity of effects were all found to be dose-related. Vomiting occurred at 0.5 and 3 mg/kg bodyweight but was more rapid at 10 or 20 mg PP796/kg bodyweight (within five minutes of dosing). Severe vomiting occurred at dose levels of 3 mg PP796/kg bodyweight and above. Diarrhoea and defecation of mucus were present in some of the animals given 1 mg PP796/kg bodyweight and above. No other treatment-related effects were observed and all dogs had recovered within six hours of dosing.

Dose req.
Efficacy
Effect on gastric emptying
Effect on Pa toxicity

The minimal effective dose level was considered to be 0.5 mg PP796/kg bodyweight, 20 mg PP796/kg bodyweight was considered to be the maximum tolerated dose (based on the severity of the clinical effects seen). The time interval between administration of PP796 and vomiting was reduced to within ten minutes by increasing the dose to 3 mg PP796/kg bodyweight and to within five minutes following doses of 10 or 20 mg PP796/kg bodyweight. However the reduction in the time taken to the initiation of vomiting was also associated with an increase in the severity of the clinical effects seen at these dose levels.

(Brammer & Robinson, 1986)

Efficacy in the presence of paraquat

The emetic action of PP796 is not impaired by the presence of paraquat. Investigations in cynomolgus monkeys (*Macaca fascicularis*) have demonstrated that the induction of vomiting by PP796 is unaffected by the presence of paraquat and that PP796 can reduce the toxicity of paraquat (Table 1).

TABLE 1: The Effect of PP796 on the Toxicity of Paraquat to the Cynomolgus Monkey

| No. of Animals | Paraquat Dose PP796 Dose | | No. Surviving |
|----------------|--------------------------|------------|---------------|
| | (mg/kg bw) | (mg/kg bw) | |
| 8 | 100 | - | 0 |
| 8 | 100 | 2 | 6 |

(Cobb *et al.*, 1979)

A further study in cynomolgus monkeys (*Macaca fascicularis*) in which the doses of both paraquat and PP796 were increased has demonstrated that PP796 is capable of effectively producing an approximately three-fold increase in the LD₁₀₀ of paraquat to the cynomolgus monkey (Table 2).

TABLE 2: The Effect of PP796 on the Toxicity of Paraquat to the Cynomolgus Monkey

| No. of Animals | Paraquat Dose PP796 Dose | | No. Surviving |
|----------------|--------------------------|------------|---------------|
| | (mg/kg bw) | (mg/kg bw) | |
| 2 | 100 | 2 | 2 |
| 2 | 250 | 5 | 2 |
| 2 | 350 | 7 | 0 |
| 2 | 500 | 10 | 0 |

(Cobb *et al.*, 1979)

In an additional study, PP796 was orally administered at 100 mg/kg bodyweight to ten male cynomolgus monkeys (*Macaca fascicularis*). Nine animals vomited between four and forty-three minutes after dosing; vomiting usually occurring twice within one hour of dosing. The remaining animal failed to vomit. Four of the ten animals

(including the animal which failed to vomit) died, all within twenty-four hours of dosing.

(Purser et al., 1978)

The effects of different oral doses of PP796 have been investigated in dogs dosed orally with 20 mg paraquat/kg bodyweight. Groups of three male dogs received an oral dose of 20 mg paraquat/kg bodyweight plus 0, 0.5, 3.0 or 20 mg PP796/kg bodyweight.

The effects of paraquat administration were assessed as follows:

- measurement of peak plasma paraquat concentrations,
- measurement of the area under the plasma paraquat concentration/time curve (AUC) and,
- grossly observable paraquat-related lung lesions at necropsy eight days after dosing.

There was a marked decrease in the peak plasma paraquat concentration, the area under the curve (AUC) and the severity of paraquat-related lung lesions of dogs dosed with either 0.5 or 3.0 mg PP796/kg bodyweight plus paraquat when compared with dogs dosed paraquat alone. These reductions were dose-related. The response in dogs dosed 20 mg PP796/kg bodyweight plus paraquat was variable, some dogs showing a reduction in the effects of paraquat whilst others showed no decrease. One dog showed evidence of increased effects of paraquat, these were considered to be due to an increased amount of paraquat having been systemically absorbed as a result of inhalation of part of the dose following regurgitation.

The effective dose range of PP796 in dogs in terms of its action in reducing the amount of paraquat which is systemically absorbed following oral ingestion, and hence its toxic effects, is considered to be between 0.5 and 3.0 mg PP796/kg bodyweight. High doses of PP796 provide no advantages over a dose of 3.0 mg PP796/kg bodyweight and may, in some dogs, be contraindicated.

(Robinson & Brammer, 1986)

3. THE EFFECT OF PP796 ON THE TOXICITY OF PARAQUAT TO EXPERIMENTAL ANIMALS

3.1 THE EFFECT OF PP796 ON GASTRIC EMPTYING

PP796 is a potent inhibitor of gastric emptying as well as being a potent oral emetic. The inhibition of gastric emptying has been demonstrated in the mouse, rat and cynomolgus monkey. The results are presented in the following table. The animals were fasted for 24 hours and then dosed with either phenol red (monkeys) or radiolabelled chromium in the form of sodium chromate (mice and rats) in the presence or absence of PP796 (administered orally or by subcutaneous injection). The animals were sacrificed after one hour and the amount of phenol red or ^{51}Cr remaining in the stomach was determined (Table 3).

TABLE 3: The Effects of PP796 on Gastric Emptying in the Mouse, Rat and Cynomolgus Monkey

| Species | Treatments | % Remaining in the Stomach |
|----------------------|---------------------|----------------------------|
| Mouse* | <u>Oral</u> | |
| | Control | 3.9 ± 0.65 |
| | 2.5 mg PP796/kg bw | 44.8 ± 4.2 |
| | <u>Subcutaneous</u> | |
| Rat* | Control | 7.1 ± 1.88 |
| | 1.0 mg PP796/kg bw | 49.4 ± 4.0 |
| | <u>Oral</u> | |
| | 1.0 mg PP796/kg bw | 16.2 ± 1.8 |
| Cynomolgus monkey ** | <u>Subcutaneous</u> | |
| | 1.0 mg PP796/kg bw | 62.4 ± 3.8 |
| | <u>Oral</u> | |
| | 0.2 mg PP796/kg bw | 33.7 ± 6.4 |
| | | 85.7 ± 4.7 |

* = non-vomiting species

** = the dose of PP796 used was 1/10th of the dose required to cause emesis and did not cause vomiting in any of the animals.

The mouse and the rat both lack the vomiting response, the effects of gastric emptying were therefore measured using doses causing vomiting in the dog and the monkey.

The inhibition of gastric emptying in monkeys was substantial, despite having been evaluated using a relatively low, sub-emetic dose.

(Wright *et al.*, 1979)

3.2 THE EFFECT OF PP796 ON THE SYSTEMIC ABSORPTION OF PARAQUAT

In rats, the administration of PP796 together with paraquat significantly delays the onset of the appearance of paraquat in the plasma and eliminates the early high peak plasma concentration which is otherwise seen in the first hour. This phenomenon results solely from the action of PP796 in inhibiting gastric emptying since the rat does not vomit. This finding therefore demonstrates that paraquat is not readily absorbed from the stomach. When PP796 and paraquat are administered to dogs and monkeys, as well as the inhibition of gastric emptying, vomiting occurs and concentrations of paraquat in the plasma are consequently much reduced.

(Wright *et al.*, 1979; Rose, 1978)

An analysis of the relationship between the concentration of paraquat present in plasma and mortality in humans reveals that those patients with paraquat blood plasma concentrations above a critical value (approximately 3 µg paraquat/ml, 24 hours after ingestion) have died. The survival of patients who accidentally (or deliberately) ingest paraquat is therefore critically dependent on the concentration of paraquat in the blood plasma during the first 24 hours after ingestion. The inclusion of PP796 in paraquat formulations leads to a considerable reduction in the concentration of paraquat in the blood plasma of dogs and monkeys and should also therefore make paraquat formulations less orally toxic to humans.

3.3 THE EFFECT OF PP796 ON THE TOXICITY OF PARAQUAT TO DOGS AND MONKEYS

A formulation containing 200 g paraquat/litre ('Gramoxone') and 0.05% w/v PP796 has been demonstrated to be between two and five times less orally toxic than a similar non-emeticised formulation when administered to dogs. The median lethal dose of the formulation containing PP796 was approximately 0.5 ml formulation/kg bodyweight (approximately 100 mg paraquat/kg bodyweight), the median lethal dose of the formulation without the emetic was between 0.1 and 0.25 ml formulation/kg bodyweight (approximately 20 to 50 mg paraquat/kg bodyweight).

(Parkinson & Lefevre, 1977)

In a similar study carried out in the cynomolgus monkey (*Macaca fascicularis*) the presence of an emetic dose of PP796 raised the LD₅₀ of paraquat (previously determined as approximately 60 to 70 mg paraquat/kg bodyweight, Purser *et al.*, 1975) to between 250 and 500 mg paraquat/kg bodyweight, thus reducing the toxicity of paraquat approximately five-fold.

(Rose, 1976)

4. EVALUATION OF THE EFFECTIVENESS OF THE ADDITION OF PP796 TO PARAQUAT FORMULATIONS ON THE TOXICITY OF PARAQUAT TO HUMANS

4.1 ESTIMATION OF THE EMETIC DOSE REQUIRED TO INDUCE VOMITING IN HUMANS

When PP796 is included in paraquat formulations in amounts sufficient to cause emesis within one hour in dogs and in monkeys, the toxicity of the formulation is significantly reduced (see Section 3.3). In order to achieve a reduction in the toxicity of paraquat formulations to humans, it is necessary to add sufficient PP796 to cause emesis, in a volume of formulation concentrate that would normally be lethal if accidentally ingested.

Human data indicates that a volume of 10 ml of a non-emeticised formulation containing 200 g paraquat/litre ('Gramoxone') represents the minimum volume which is potentially lethal to humans. It has been concluded that a concentration of 5 mg PP796 in 10 ml of 'Gramoxone' (i.e. 0.05% w/v) should be added to the formulation in order to ensure that a person ingesting the lowest potentially lethal volume (10 ml) receives an effective dose of emetic. This dose is estimated to induce vomiting within an hour in a person ingesting 10 ml or more of 'Gramoxone'.

(Rose, 1977)

4.2 ROLE OF PP796 IN THE REDUCTION OF FATALITIES ARISING FROM THE ACCIDENTAL ORAL INGESTION OF PARAQUAT FORMULATIONS

For obvious reasons it is not possible to carry out a study to specifically determine the effect of the addition of PP796 on the toxicity of paraquat formulations to humans. Epidemiological data, can however provide reliable information on the effectiveness of the emetic when such data is based on accurate records of cases involving paraquat poisoning. The UK National Poisons Information Service (NPIS) provides a reliable source of information on paraquat poisonings in the UK.

Published data from the NPIS based on UK incident data collected in the early 1980s suggested that the presence of PP796 in paraquat formulations may be associated with some reduction in mortality rates following the ingestion of paraquat formulations.

(Denduyts-Whitehead et al., 1985)

The UK NPIS data has been reviewed more recently with the following conclusions. Paraquat formulations containing PP796 cause both a more reliable and an increased incidence of vomiting within half an hour of ingestion than paraquat formulations without emetic. The addition of PP796 to paraquat formulations may therefore have some value in preventing serious poisoning when the amounts ingested are relatively small (< 25 ml 'Gramoxone'), i.e. in those cases involving accidental ingestion. However, in cases of deliberate oral ingestion with suicidal intent, circumstances in which relatively large (>25 ml 'Gramoxone') volumes are swallowed, a beneficial effect of the inclusion of the emetic on survival rates could not be demonstrated.

This is presumably because even after emesis has occurred the amount of paraquat present in the gastrointestinal tract is still sufficient to result in a fatality. Suicides, by whatever means are a tragic occurrence but for paraquat and other chemical means (agrochemicals, pharmaceuticals and other household chemicals) this represents gross abuse of a product which when used for its legitimate purpose brings significant benefits to society.

ZENECA Agrochemicals' experience in the UK and indeed, worldwide, is that the combination of preventive measures adopted, including the formulation additives of stench, dye and an effective emetic have resulted in a significantly decreased incidence of fatalities occurring as a result of the accidental oral ingestion of paraquat formulations.

(Calderbank, 1992)

REFERENCES

1. Bayliss, P F C
A summary of clinical results of the phosphodiesterase inhibitor ICI 63197 in a variety of disease states
ICI Pharmaceuticals Division Report No. PH20992B
1973
2. Case, D E; Dunlop, D
The intravenous administration of ICI 63197 to beagle dogs
ICI Pharmaceuticals Division Report No. PH23517C
1977
3. Foulkes, D M
Compound PP796 : mode of action as an emetic
ICI Jealott's Hill Research Station
July 1978 **3E.2/1**
4. Cobb, L M; Purser, D A; Coombs, D W; Grimshaw, P
The acute oral toxicity and mode of action of emetic PP796 in cynomolgus monkeys, and its effect upon the acute oral toxicity of several formulations of paraquat
Huntingdon Research Centre Report No. ICI 119/78556
19 March 1979 **3B.1/13**
5. Purser, D A; Grimshaw, P; Cobb, L M
The toxicity of orally administered emetic PP796 in cynomolgus monkeys
Huntingdon Research Centre Report No. ICI 171/78627
8 November 1978 **3B.1/11**
6. Brammer, A; Robinson, M
PP796: emetic dose response study in dogs
ICI Central Toxicology Laboratory Report No. CTL/T/2459
6 March 1986 **3B.1/18**
7. Robinson, M; Brammer, A
PP796: emetic study in paraquat treated dogs
ICI Central Toxicology Laboratory Report No. CTL/T/2471
6 March 1986 **3B.1/19**
8. Wright, A F; Wyatt, I; Rose, M S
The effect of PP796 on gastric emptying in rats, mice and monkeys and on paraquat absorption in rats
ICI Central Toxicology Laboratory Report No. CTL/R/489
19 October 1979 **3E.2/4**

9. Rose, M S
The effect of PP796 on paraquat toxicity
ICI Central Toxicology Laboratory Letter Report
10 August 1978 **3E.2/2**
10. Parkinson, G R; Lefevre, V K
Paraquat : comparison of the oral toxicity to the dog of the two
formulations JF 1682B and JF 6043
ICI Central Toxicology Laboratory Report No. CTL/P/362
11 October 1977 **3D.1/2**
11. Purser, D A; Hardy, C J; Clark, G C; Cobb, L M
The toxicity of orally and intravenously administered paraquat
dichloride in cynomolgus monkeys
Huntingdon Research Centre Report No. ICI 50/74938
27 January 1975 **3B.1/15 (paraquat)**
12. Rose, M S
The effect of administration of an emetic (PP796) on paraquat
toxicity in dog and monkey
ICI Central Toxicology Laboratory Report No. CTL/R/391
November 1976 **3E.1/2**
13. Rose, M S
The concentration of PP796 required to produce emesis in experimental
animals and an estimation of the emetic dose in man
ICI Central Toxicology Laboratory Report No. CTL/R/390(R)
February 1977 **3B.1/3**
14. Denduyts-Whitehead, A P; Hart, T B; Volans, G N
Effects of the addition of an emetic to paraquat formulations on
acute poisoning in man
J. Toxicol. Clin. Toxicol.
Volume 23, pp 422 - 423 (1985)
15. Calderbank, A
'Gramoxone' poisoning in the UK 1980-1988 and the role of the emetic
ICI Agrochemicals Report No. ODM50 AC/RB
October 1992

Prepared 10/10/97.
for Helen Boya to read to Nigeria

A Case For Inclusion Of The Emetic PP796 In Paraquat Formulations

To whom it may concern

Zeneca include the emetic PP796 [2-amino-6-methyl-5-oxo-4-n-propyl-4,5-dihydro-5-triazolo (1,5-a) pyridine) in paraquat formulations. The following details the characteristics of PP796 as a suitable emetic in these formulations

1. It must be rapidly absorbed

PP796 is rapidly absorbed in mammals (rats, dogs and monkeys) following oral ingestion. Peak plasma levels, which are dose-dependent, being observed in man during the first hour after administration (Bayliss 1983).

2. It must be a strong emetic and quick acting with a limited 'action period'

In species which vomit such as dogs and man, the rise in PP796 plasma level is associated with the onset of vomiting. This has been demonstrated to occur within 15 minutes of dosing. Vomiting may be repeated four or five times within the first hour. PP796 is thus a potent oral emetic and man is sensitive to its action. After the full hour the effect ceases, probably as a consequence of the rapid metabolism and excretion of the compound (Case and Dunlop 1977).

3. It must not be a gastric irritant

A major attraction for the use of PP796 is that its mode of emesis action is not by gastric irritation; this would be a major disadvantage with paraquat as this might increase absorption. The action of PP796 is actually centrally mediated and evidence for this is provided by 1) the rapid onset of vomiting (and absence of irritant effects) and 2) the production of vomiting in dogs following intravenous administration at plasma levels similar to those producing the effect after oral administration (Case and Dunlop 1977).

4. It must be toxicologically acceptable

As human exposure to PP796 will occur as a consequence of the deliberate ingestion of Gramoxone or other paraquat containing products it must not present toxicological effect. A wide range of studies have been completed with PP796 using oral dosing or dietary administration to assess the toxicological significance of this route of exposure.

Acute Oral Toxicity

The acute oral MLD value of PP796 in rats is 100-150mg/kg (Anon 1983, Davison and Smith 1988). The acute oral toxicity in mice is 300mg/kg (Anon 1983).

Skin Irritation

PP796 is a slight skin irritant and is not a strong skin sensitizer (Moses 1979).

Subchronic Oral Toxicity

Dietary administration of PP796 in rats (5mg/kg/day) and dogs (1.5mg/kg/day) for three months has been investigated. In rats there were no treatment related effects on

hematology, organ weights or histopathology. Similarly in dogs, PP796 caused no adverse effects on hematological, biochemical or histopathological parameters. In addition, blood pressure, heart or respiration rate and measured ECG-activity remained unaffected by PP796 treatment. At the end of the dosing period a number of top dose animals were placed on a normal diet ie without PP796, for up to 12 weeks. There were no changes in these animals attributable to PP796 (Anon 1983).

Teratogenicity

PP796 has no teratogenic effects and no significant effects on pregnancy, littering or weaning in rats and rabbits given daily doses of up to 1.25mg/kg/day (Anon 1983).

These data demonstrate that PP796 presents no acute risk to humans and is acceptable, based on its toxicology, for use as an emetic in paraquat formulations.

5. It must be compatible and stable in paraquat formulations

While CTL cannot comment on the herbicidal efficiency of PP796 formulated paraquat, its compatibility and stability have been demonstrated in dogs exposed to either PP796 alone, PP796 in blank formulation or PP796 in paraquat formulation, where there were no differences in emetic response between studies (Brammer and Robinson 1986, Robinson and Brammer 1986, Collins and Robinson 1986). In addition, studies in rats, mice and monkeys have shown it to have a delaying effect on gastric emptying, and since most paraquat swallowed is absorbed from the small intestine the resulting inhibition of absorption may make a useful contribution in the period immediately following ingestion (Wright et al 1979). Indeed, studies in dogs have shown reductions in subsequent paraquat absorption/effects in emeticised formulations compared with non-emeticised-paraquat (Robinson and Brammer 1986a). Furthermore, Zeneca's own experience and anecdotal evidence indicates that the emetic improves the survival of patients who have swallowed small doses through its combined effects of dose reduction and rapid hospitalization. The survival rate in patients who have accidentally ingested paraquat has been very good.

References

Bayliss PFC

A summary of clinical results of the phosphodiesterase inhibitor ICI 63197 in a variety of disease states

Zeneca Pharmaceuticals Division Report No PH20992B 1973

Case DE, Dunlop D

The intravenous administration of ICI 63197 to beagle dogs

Zeneca Pharmaceuticals Division Report No PH23517C 1977

Cobb LM, Purser DA, Coombs DW, Grimshaw P

The acute oral toxicity and mode of action of emetic PP796 in cynomolgus monkeys and its effect upon the acute oral toxicity of several formulations of paraquat

Huntingdon Research Centre Report No ICI 119/78556 1979

Davison V, Smith LL

PP796 Acute oral toxicity to the rat

Zeneca Central Toxicology Laboratory Report No CTL/L/2034 1988

Moses SE

Skin and eye irritation, skin sensitization potential and respirable fraction analysis

Zeneca Central Toxicology Laboratory Report No CTL/T/1277 1979

Anon

Safety Evaluation Results

Pharmaceuticals Division Report No. ICI63197 1983

Robinson M, Brammer A

PP796 Emetic study in paraquat treated dogs

Zeneca Central Toxicology Laboratory Report No CTL/T/2471 1986

Brammer A, Robinson M

PP796 Emetic dose response study in dogs

Zeneca Central Toxicology Laboratory Report No CTL/T/2459 1986

Collins MA, Robinson M

PP796 Emetic Efficacy in a blank paraquat formulation

Zeneca Central Toxicology Laboratory Report No CTL/L/1359 1986

Wright AF, Wyatt I, Rose MS

The effect of PP796 on gastric emptying in rats, mice and monkeys and on paraquat absorption in rats

Zeneca Central Toxicology Laboratory Report No CTL/R/489 1979

Emetic's

From: Shaunak Richa R Date: 30-May-1997 15:18
6=Shaunak@8=R@4=GBJHA@5=Agrochemicals@3=ZENECA@2=TMAILUK@1=GB@7=Rich
TO: Joseph A. Wilson (WILSON JA@A1@UWZ00)
CC: Scott Bob RC @APVXC (SCOTT RC@A1@APVXC1)
CC: Cook Andy AR @FHVAX (COOK AR@A1@FHVAXC)
Subject: RE: Emetic Levels in Paraquat Finished Products

Joe,

Apologies for the delay in getting back to you. Yes, I'm still working on paraquat products!!

I'm afraid I don't have any documents myself, but Bob Scott (CTL), and/or Andy Cook, (Regulatory Affairs, Fernhurst) may be able to help.

I've copied this note to both of them, but it may be worthwhile your contacting them direct.

Cheers
Richa

From: Joseph A. Wilson
To: Shaunak Richa R@MSMAIL
Subject: Emetic Levels in Paraquat Finished Products
Date: 20 May 1997 15:05

Richa,

I hope that you are doing well. Are you working on paraquat products? I was wondering if there are documents explaining the logic for the amount of emetic (PP-796) that is used in paraquat finished products. If there are, would you please forward them to me. Thank you.

Cheers,
Joe

Bob - would he be attached for me too?

'TO WHOM IT MAY CONCERN

PP796 EMETIC

In considering the properties of PP796 in comparison with other emetics it is necessary to first consider the criteria which an emetic must meet in order to be appropriate for inclusion in paraquat formulations.

1. Speed and mode of action

The emetic must produce a rapid vomiting response prior to the absorption of toxic amounts of paraquat. It should act centrally and should not produce its action via an irritant effect on the gastric system; irritancy could facilitate the absorption of paraquat.

2. Specificity

The agent must be able to act in the presence of paraquat, i.e. appropriate animal experiments must provide evidence that paraquat does not interfere with the action of the emetic.

3. Human safety

The emetic should be toxicologically acceptable and harmless to the user of the product in which it is incorporated.

4. Environmental safety

The emetic should not have a harmful effect on the environment.

5. Stability

The emetic must be stable in the presence of paraquat and vice versa. The emetic should not interfere with the herbicidal properties of paraquat.

An assessment was made of the following candidate emetic agents, most of which were excluded on the basis that they did not meet one or more of the necessary criteria.

1. Matricaria

This is the ground flower heads of the chamomile plant. It is irritant in action, unreliable and, being insoluble in water, would be of no practical value for use in paraquat formulations.

2. Mustard

This is also highly irritant and insoluble.

3. Salts of heavy metals (eg. copper, antimony and zinc)

These agents are firmly rejected by modern medical opinion because of their high toxic risk. They would also be unacceptable from an environmental perspective.

4. Sodium chloride

This emetic, commonly used in domestic poisoning incidents, is no longer generally recommended by the medical profession. Its efficacy is variable and a number of deaths have occurred following its use.

5. Apomorphine

This agent, although highly effective, can only be administered by intramuscular injection. It is unstable in air. It is therefore clearly of no practical value for inclusion in paraquat formulations.

6. Ipecacuanha

This agent is widely used as an orally administered emetic, it acts on the central nervous system but is also a gastric irritant. When administered in excessive amounts (approximately 10 x the emetic dose) fatalities have occurred. This emetic was seriously considered by ICI for inclusion in paraquat formulations but a study in cynomolgus monkeys found that the response was unpredictable and only effective at doses associated with toxic symptoms.

7. PP796

PP796 is rapidly absorbed in mammals following oral ingestion, peak plasma levels being observed in man during the first hour after administration. In species which vomit such as pig, dog, monkey and man (rodent species do not vomit) the rise in plasma level is associated with the onset of vomiting. This generally occurs within 15 minutes of dosing. Vomiting may be repeated four or five times within the first hour. Thereafter the effect ceases, probably as a consequence of the rapid metabolism and excretion of the compound. The evidence for the action of PP796 being centrally mediated is provided by 1) the rapid onset of vomiting and absence of irritant effects and 2) the production of vomiting in dogs following intravenous administration at plasma levels similar to those producing the effect after oral administration.

PP796 is an extremely potent oral emetic, with man particularly sensitive to its action. A dose of only 0.1 mg/kg is sufficient to produce a 75% expectancy of vomiting in man. Furthermore investigations in monkeys have demonstrated that the induction of vomiting by PP796 is unaffected by the presence of paraquat.

In clinical studies emesis occurred at doses in the range 0.03-0.11 mg PP796/kg (equivalent to 2-8 mg for a 70 kg man). Statistics of paraquat poisoning incidents indicate that most have involved the ingestion of more than 20 ml 'Gramoxone'. Inclusion of PP796 at a rate of 0.05% (5 mg in 10 ml or 0.5 g in 1 litre) is therefore likely to cause vomiting in those ingesting this quantity or above.

In addition to its action as an emetic PP796 has a second property which makes it particularly suitable for inclusion in paraquat formulations as a safening agent. PP796 has been shown to have a delaying effect on gastric emptying, since most paraquat swallowed is absorbed from the small intestine the resulting inhibition of absorption may make a useful contribution in the period immediately following ingestion.

Thus the question of the effectiveness of PP796 in comparison with other emetics is more an issue of which emetics are able to meet the exacting characteristics required rather than a straightforward comparison of the speed with which they are able to induce emesis.

ICI is committed to reductions in the hazard of paraquat formulations and the inclusion of the emetic is an important part of this worldwide. It is usually not practically possible to obtain definitive epidemiological data on the effectiveness of the emetic since accurate information on the quantity ingested and the time between ingestion and treatment is seldom available. ICI's own experience and anecdotal evidence indicates that the emetic improves the survival of patients who have swallowed small doses through its combined effects of dose reduction and rapid hospitalisation. The survival rate in patients who have accidentally ingested paraquat has been very good. However in patients who have ingested large doses survival continues to be poor since the dose ingested is so great that in spite of the emesis induced sufficient paraquat is still present to cause a fatality.'

Pq1 Emetics

From: Julie Mitchell
MITCHELL JA2

Date: 27-Mar-1997 09:58

TO: Davis M T
CC: Sutcliffe H A
CC: Cook A R
CC: Bob Scott - CTL

(DAVIS MT@A1@FHVAXC)
(SUTCLIFFE HA@A1@FHVAXC)
(COOK AR@A1@FHVAXC)
(SCOTT RC)

Subject: Paraquat Emetics

Martin,

Thankyou for your request of the 14th January 1997. While there appear to be a wealth of data regarding post-poisoning treatment with emetics, very little have been published on the use of emetics formulated with Paraquat as a means of reducing toxicity should accidental poisoning occur. Moreover, there appear not to be any public reference made to the Paraquat product trading as Agazone.

It seems that, apart from the extensive work carried out on the old Pharmaceutical's product, PP796, CTL have only looked at the emetic effects of Ipecacuanha. The usefulness of Ipecacuanha as a Paraquat formulant emetic was dismissed since it was found to be unpredictable and only effective at toxic doses when tested in cynomolgus monkeys (1).

Standard toxicity studies rather than emetic efficiency/efficacy studies were carried out on the other emetics seen at CTL.

Research into the effects of monoclonal antibodies on subsequent Paraquat toxicity have also been investigated and are now published (2-3); these data indicate that these studies have no benefit in vivo.

According to a February 1995 document put together at Fernhurst entitled "91/414/EEC Review of Paraquat Dichloride under Regulation 3600/92", which I believe formed part of the EU monograph, a number of possible emetics (matricaria; mustard; salts of heavy metals eg copper, antimony and zinc; sodium chloride, apomorphine and ipecacuanha) have been considered and rejected on various grounds of unsuitability: the CTL database can add nothing to these summations.

Extensive interrogation of external sources revealed only two references pertinent to your enquiry (4-5), which have been ordered and are due to arrive within the next few weeks). Also retrieved was a copy of the European Patent Application for Paraquat and Diquat, prepared by Jon Heylings, which cites the UK Patent 1507407 for emetic inclusion (6). I believe that Martin Wilks will have a copy of the former document, however, please let me know if you would like me to forward you a copy.

Reference to analytical methods also proved elusive. Three papers have been identified (7-9) which may hold some relevance to your enquiry. I have ordered copies and will send you an update when they become available.

Cost and time constraints dictated that the above search be kept very general although we believe all papers associating Paraquat and emesis have been retrieved. We did, however, identify quite a list of specific emetics all of which can be searched against with regards to their presence, identification and effectiveness in herbicide formulations. I will forward copies (via the post) of the STN registry printouts for these for you to consider and then we can agree whether to proceed with some or all of them. I believe, however, that this could prove to be costly with little return.

Although this task is not yet complete, can we please discuss again any future needs when these data are available.

Kindest Regards
Julie

References

- 1) Anon
Ipecacuanha: The emetic activity of liquid extract of Ipecacuanha BP in cynomolgus monkeys; Emetic response
CTL/C/727
[Confidential to Zeneca Agrochemicals]
- 2) Wright AF, Green TP, Daley-Yates P, Smith LL
Monoclonal antibody does not protect mice from paraquat toxicity
Vet Hum Toxicol 29(Suppl 2) 102 1987
- 3) Wright AF, Green TP, Robson RT, Niewola Z, Wyatt I, Smith LL
Specific polyclonal and monoclonal antibody prevents paraquat accumulation into rat lung slices
Biochem Pharmacol 36(8) 1325-1331 1987
- 4) Houpt K, Zgoda JC, Stahlbaum CC
Use of taste repellants and emetics to prevent accidental poisoning of dogs
Am J Vet Res 45(8) 1501-1503 1984
(Ordered 13/3/97)
- 5) Yamashita K, Yoshida M
Agrochemicals formulated to prevent intake by humans
Jpn Kokai Tokkyo Koho 6pp 1987
(Ordered 13/3/97)
- 6) Heylings JR
Bipyridilium herbicide formulations safened for humans
Eur Pat Appl 467529 1992
- 7) Erhardt PW, Smith RV, Sayther TT, Keiser JE
Thin layer chromatography of apomorphine and its analogues
J Chromatograph 116(1) 218-224 1976
- 8) Verpoorte R, Svendsen AB
Thin layer chromatography versus high pressure liquid chromatography in the analysis of alkaloids
Zentralbl Pharm Pharmakother Laboratoriumsdiag 118(6) 563-571 1979
- 9) Sahu NP, Mahato SB
Determination of emetine and cephaeline in Ipecac roots by high performance liquid chromatography
J Chromatograph 238(2) 525-529 1982

Scott Bob RC - CTL

From: Scott Bob RC - CTL
Sent: 08 October 1997 15:53
To: Davis Martin MT
Cc: Mitchell Julie JA
Subject: ID PQ threat to registration
Importance: High

Martin,

I have the following response to your query.

It is always difficult to obtain definitive data on the effectiveness of the emetic. Zeneca (then ICI) recognised the need to improve the safe handling of PQ formulations in the mid to late '70's and forged ahead with a 3 pronged approach to improve this situation ie emetic, stench and dye. All 3 were added to formulations at the same time at it is not possible to provide definitive data to support the merits of each additive.

I am encouraged, however, by the data cited in the paper from Yamashita et al (Vet Hum Tox, Supplement, p48-49, 1982) on the effect of the emetic in altering plasma levels of paraquat in dogs. In CTL we believe that in the absence of human data the dog is a very robust model to predict human paraquat kinetics.

In this study, dogs were dosed at 30 mg/kg paraquat both with and without emetic. This dose level was chosen as the authors claimed this was the MLD : my own experience is that this is on the high side and the MLD is nearer 10 mg PQ/kg (perhaps the authors are referring to formulated product or technical material?)

At this dose level the PQ levels in dogs were significantly lower in the dogs given the emetised paraquat compared with those not given the emetic. As no mortality data have been presented it must be assumed that the plasma levels are indicative of toxicity : a view supported by CTL. The only conclusion which can be reached is that the emetic is effective in reducing oral toxicity: extrapolation to survival is more difficult but this must give a better prognosis.

The effect of the emetic on vomiting time is more difficult to determine. It appears that vomiting occurs earlier with the emetic than without : the presentation of these data is confused.

At higher paraquat dose levels the effect of the emetic is less clear. The higher dose groups were given 8 times the MLD dose. No data can be interpreted to clarify the time or effectiveness of vomiting in the emetised and non-emetised paraquat doses. It is possible that at these dose levels any emetic would be ineffective as the emesis process would not be 100% effective and a supra-MLD would still remain in the stomach/gi tract: thus no difference in plasma levels, as seen.

I believe that the data in this paper from Yamashita et al indicate that in the reported experiments the emetic would be effective in reducing oral toxicity in dogs when present in paraquat-containing products.

These data are consistent with our own experience in dogs at CTL. The emetic is effective in inducing earlier emesis in paraquat-containing products compared with non-emetised paraquat. The time of vomiting and the extent of eesis is decreased and increased, respectively, as the dose of emetic is increased. It has also been established that too high a dose of emetic can reduce the safety of formulations, presumably by causing too dramatic vomiting with the opportunity to damage the gi tract lining or deliver vomit containing in to the lungs.

I hope this is useful in your response, contact me if you need more,

Bob.

TOXICOLOGIE CLINIQUE

Facteurs pronostiques de l'intoxication aiguë par le paraquat. Etude rétrospective sur les cas enregistrés au Centre Anti-Poisons de Paris en 1981**XX^{èmes} journées du Groupement Français des C.A.P.
Bordeaux - 30 Septembre-1er Octobre 1982****FRELON J-H.*, MERIGOT P.*, GARNIER R.*, BISMUTH C.*,
EFTHYMIU M-L.*.**

* Centre Anti-Poisons de PARIS et Clinique Toxicologique
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Résumé :

Près de vingt ans après la publication des premières observations, l'intoxication par le paraquat demeure de sombre pronostic en raison de l'absence de traitement efficace. En revanche, les travaux de plusieurs équipes ont permis de définir des facteurs pronostiques. Récemment, BISMUTH et Coll(2) ont démontré que les critères de gravité suivants étaient significatifs : la voie d'absorption digestive, l'existence de lésions gastriques, l'insuffisance rénale organique, la concentration plasmatique de Paraquat.

Sur une série d'observations enregistrées au centre anti-poisons de Paris en 1981, nous avons entrepris d'étudier l'intérêt pronostique des paramètres suivants : voie d'administration, sexe, circonstances de l'intoxication, quantité ingérée, concentration de la solution, existence d'un émétisant, état de réplétion gastrique, lésions caustiques digestives (bouche, œsophage, estomac), insuffisance rénale, perturbations du bilan hépatique, gazométrie, épreuves fonctionnelles respiratoires, dosages sanguin et urinaire de Paraquat. 41 appels concernant le paraquat ont été enregistrés pendant cette période, dont 34 en rapport avec une intoxication aiguë chez l'homme. Dans 27 cas, il s'agit d'une intoxication aiguë par voie digestive, accidentelle (9 cas dont 2 décès) ou volontaire (18 cas dont 18 décès), sur lesquels nous avons réalisé notre étude (les autres appels portant sur 2 projections oculaires, 4 inhalations et 1 projection cutanée).

L'intérêt de cette nouvelle enquête réside dans les particularités de notre échantillon. En raison de notre recrutement, en effet, la population étudiée est sensiblement différente de celles des séries déjà publiées : répartition géographique plus large de patients, plus grande diversité des circonstances, des voies d'entrée, des quantités d'herbicide absorbées, des traitements entrepris, etc... Cette étude confirme la validité des critères de gravité définis par BISMUTH et coll(2). Les paramètres qui apparaissent significatifs sont strictement liés à la quantité ingérée. Sur cette plus large série, nous avons pu mettre en évidence une plus grande sévérité des intoxications volontaires. Nous avons par ailleurs constaté,

- d'une part, dans certains cas, une aggravation des lésions caustiques digestives, que peut méconnaître une fibroscopie trop précoce et qui justifie, semble-t-il, un contrôle systématique à la 48^{ème} heure,
- d'autre part, l'impossibilité d'extrapoler au-delà de la 24^{ème} heure la courbe prédictive de PROUDFOOT(16).

Mots-clés : PARAQUAT - FACTEURS PRONOSTIQUES.

TOXICOLOGIE CLINIQUE

Prognostic factors of acute paraquat poisoning. Retrospective study of the cases collected in 1981 at the Poison Control Center of Paris

Summary :

Twenty years after the publication of the first cases, the intoxication with the herbicide Paraquat still has a low prognosis because of no efficient treatment. But many studies have allowed the definition of prognostic factors. Nearly, BISMUTH and als(2) demonstrated that the following criteria are significant : the oral route, the gastric lesions, the organic renal failure, the plasma-Paraquat concentration.

Through a series of cases collected in 1981 at the Poison Control Center of Paris, the following prognostic factors have been studied : route of administration, sex of patient, circumstances of the poisoning, ingested volume, concentration of the solution, existence of an emetic in the commercial solution, gastric content, lesions of the upper digestive tract (mouth, oesophagus, stomach), renal impairment, hepatic failure, blood gazometry, lung function tests, plasma and urine paraquat concentrations. Forty-one cases were collected during this period, with thirty-four concerning acute Paraquat poisonings in humans. We studied twenty-seven of them caused by acute oral poisoning, with accidental circumstances in nine cases (two died) and intentional circumstances in eighteen cases (all died) (other cases concerned two ocular projections, four inhalations and one skin projection).

The interest of this new investigation is the particularity of our series. Because of our recruitment (larger geographic distribution of patients, larger diversity of circumstances, of routes of administration, of ingested quantities, of treatments...). This series of cases is quite different from others previously published. This study confirms the validity of prognostic factors defined by BISMUTH and als(2). The factors, which look significant, strictly depend on the ingested quantity.

Through this larger series of cases we could see that the intentional poisonings were more serious.

We could also establish :

- on the one hand, sometimes, a worsening of the digestive caustic lesions, which can be ignored by an early digestive fibroscopic examination and which requires another examination at the second day.
- on the other hand, the present impossibility of extrapolating the predicting line of PROUDFOOT(16) after the twenty-fourth hour.

Key-words : PARAQUAT - PROGNOSTIC FACTORS.

L'intoxication par le paraquat (1, 1' diméthyl 4, 4' bipyridilium dichlorure), herbicide largement utilisé, demeure toujours de sombre pronostic, près de vingt ans après la publication des premières observations, en raison de l'absence de traitement efficace.

En revanche, les travaux de plusieurs équipes ont permis de définir des facteurs pronostiques :

- Proudfoot(15), en 1979, en précisant la valeur pronostique de la concentration sanguine de Paraquat dans les 24 premières heures.

- Bismuth et coll.(2), qui, récemment, ont démontré que d'autres facteurs étaient significatifs : voie d'absorption digestive, existence de lésions gastriques, insuffisance rénale organique, concentration plasmatique de paraquat.

Sur une série d'observations enregistrées au Centre Anti-Poisons de Paris (C.A.P.P.) en 1981, nous avons entrepris d'étudier rétrospectivement l'intérêt pronostique de ces facteurs de gravité. L'intérêt de cette nouvelle enquête réside dans les particularités de notre recrutement (répartition géographique plus large des patients, plus grande diversité des circonstances, des voies d'entrées, des quantités absorbées, des traitements entrepris). La population étudiée est ainsi sensiblement différente de celle des séries déjà publiées, en particulier celles constituées d'intoxications hospitalisées en milieu de réanimation et, de ce fait, presque toujours sévères.

MATERIEL ET METHODES

41 appels concernant le paraquat ont été enregistrés au C.A.P.P. en 1981.

Nous avons exclu de cette étude 14 observations :

- 3 intoxications animales
- 1 question sur la tératogénicité du paraquat
- 2 observations dont la symptomatologie n'était pas en rapport avec le produit
- 1 demande d'expertise judiciaire
- 7 intoxications par voie extra-digestive (2 projections oculaires, 4 inhalations et 1 projection cutanée), toutes d'évolution favorable.

C'est donc sur 27 intoxications aiguës par voie digestive qu'a porté notre étude.

Elle se répartissent en :

- 18 intoxications volontaires (17 adultes - 1 enfant)
- 9 intoxications accidentelles (6 adultes - 3 enfants)

L'âge moyen de l'intoxiqué, toutes circonstances confondues, est de $33,69 \pm 20,4$ (5 à 73 ans).

Nous avons observé une fréquence importante (5 cas sur 18) des intoxications volontaires aux Antilles (Guadeloupe - Martinique).

Les types de produits en cause étaient : GRAMOXONE dans 12 cas - GRAMOXONE 2 dans 13 cas - PRIGLONE 2 (PARAQUAT 12 % - DIQUAT 8 %) dans 2 cas.

Les circonstances de décès ont été :

- pour les intoxications volontaires (18 décès sur les 18 observations) :
 - arrêt cardio-vasculaire dans 15 cas (de la 9ème heure au 6ème jour)
 - insuffisance rénale organique dans 1 cas (4ème jour)
 - hémorragie digestive dans 1 cas (12ème heure)
 - péritonite dans 1 cas (24ème heure)

- pour les intoxications accidentelles (2 décès sur 9 observations) : par fibrose pulmonaire (8ème jour et 24ème jour).

Nous avons entrepris d'étudier l'intérêt pronostique des paramètres suivants :

- sexe,
- circonstance de l'intoxication (volontaire ou accidentelle),
- quantité ingérée (moins d'une gorgée, supérieure ou égale à une gorgée),
- concentration de la solution,
- présence d'un émétisant dans la solution commerciale,
- état de réplétion gastrique,
- lésions caustiques digestives (bouche, œsophage, estomac, par un examen endoscopique),
- insuffisance rénale (créatinine sanguine et urinaire - clairance de la créatinine - ionogramme sanguin et urinaire),
- perturbation du bilan hépatique,
- gazométrie (HbO₂, pH, Pa O₂, Pa CO₂),
- épreuves fonctionnelles respiratoires (capacité vitale, volume résiduel, VEMS, DLCO et compliance),
- dosages sanguins et urinaires de paraquat.

Le test statistique utilisé est le Khi deux (avec la correction de Yates pour les petits effectifs).

RESULTATS ET DISCUSSION

1 - sexe

Les intoxiqués sont 20 hommes (dont 13 sont décédés) et 7 femmes, toutes décédées. Ce critère n'apparaît pas significatif ; la plus grande proportion d'intoxications masculines s'explique par une manipulation plus fréquente du produit chez l'homme.

2 - circonstances de l'intoxication

Sur nos 27 observations, l'intoxication a été volontaire dans 18 cas, dont 18 décès et accidentelle dans 9 cas, dont 2 décès.

Dans notre étude, ce critère apparaît très significatif ($p < 10^{-5}$). Il est en fait directement lié à la quantité ingérée, habituellement beaucoup plus importante en cas d'intoxication volontaire que lors d'ingestion accidentelle du produit.

Ce paramètre n'avait pas de valeur pronostique dans la série de Bismuth et coll.(2) constituée d'intoxications hospitalisées en milieu de réanimation et, du fait de ce recrutement, presque toujours sévères.

3 - quantité ingérée

L'étude de Pasi(14) a estimé la dose létale minimum de Paraquat (pour un adulte de 70 kg) à 35 mg/kg. Une gorgée de la solution concentrée à 20 % (55 mg/kg) est potentiellement mortelle. Une gorgée de la solution à 12 % représente 30 mg/kg.

Dans notre étude, 4 patients ont absorbé une quantité inférieure à 1 gorgée : un seul d'entre eux est décédé (au 4ème jour d'une insuffisance rénale organique).

19 patients ont absorbé une quantité égale ou supérieure à 1 gorgée (de 40 ml à 200 ml) ; 16 d'entre eux sont décédés ($P < 0,05$). Parmi ces 19 patients :

- 4 ont absorbé une quantité égale à 1 gorgée (40 ml) ; un seul est décédé (de fibrose pulmonaire au 24ème jour),
- 15 ont absorbé une quantité supérieure à 1 gorgée ; ils sont tous décédés (14 d'arrêt cardio-vasculaire entre la 9ème heure et le 6ème jour ; un, de péritonite, à la 24ème heure),
- pour 4 patients (dont 3 sont décédés), la quantité absorbée est inconnue.

Ainsi, dans notre expérience, l'absorption d'une quantité inférieure à une gorgée à une mortalité de 25 %. Celle d'une quantité égale ou supérieure à une gorgée à une mortalité de 84,2 % ; la mortalité étant de 100 % quand la quantité est supérieure à une gorgée.

4 - concentration de la solution

Dans notre étude, 23 patients (dont 19 sont décédés) ont absorbé la solution concentrée à 20 % ; 2 patients (dont 1 est décédé) ont absorbé la solution à 12 %. Dans 2 cas, d'évolution favorable, les patients avaient absorbé une solution à 20 % diluée.

Nous ne retrouvons pas de différences significatives entre la solution à 12 % et celle à 20 %, mais notre échantillon de patients ayant absorbé la solution à 12 % (2 cas) est trop faible.

5 - présence d'un émétisant

La notion de la présence ou non d'un émétisant dans la solution commerciale ne nous est connue que dans 3 cas ; ce qui là encore ne permet pas de conclure.

6 - état de réplétion gastrique

L'étude de ce critère repose sur la notion de l'inactivation du produit au contact du sol(3). La moindre gravité des intoxications en cas d'ingestion sur estomac plein a été signalée, pour la première fois, par Matthew(11) en 1971, bien que le rôle protecteur des aliments n'ait jamais été prouvé chez l'animal. C'est aussi sur cette notion que repose l'administration de terre de Fuhler ou d'un adsorbant(13-14-17).

Dans notre étude, il n'y a pas eu, dans 10 observations, de prise alimentaire dans les heures qui ont précédé l'intoxication ; 9 de ces patients sont décédés. Dans 7 cas, l'absorption de paraquat s'est faite sur estomac plein : 5 de ces patients sont décédés.

Dans 10 cas, l'état de réplétion gastrique nous est inconnu.

Nous n'avons pas retrouvé ici de différence significative, mais, dans beaucoup d'observations, la quantité de paraquat ingérée est importante, sûrement bien supérieure à celle que peuvent inactiver les aliments contenus dans l'estomac.

7 - lésions caustiques digestives

Une fibroscopie systématique a été réalisée chez 15 patients entre la 3ème heure et le 5ème jour. L'absence de fibroscopie dans 12 observations s'explique très souvent par l'hospitalisation du patient dans un hôpital périphérique ou d'Outre-Mer, où cet examen ne peut être réalisé en urgence.

A l'entrée, des lésions buccales ont été notées chez 5 patients (tous décédés) ; chez 7 patients (dont 2 sont décédés) l'examen ORL était normal, alors que 3 d'entre eux présentaient des lésions œso-gastriques à la fibroscopie.

Pour 15 patients (dont 13 sont décédés), l'existence de lésions buccales nous est inconnue, alors qu'une fibroscopie pratiquée chez 8 d'entre eux montrait des lésions œso-gastriques.

La fibroscopie digestive montrait :

1) des lésions œsophagiennes chez 10 patients (dont 7 sont décédés) et l'absence de lésions œsophagienne chez 2 patients (dont 1 est décédé). Ces 2 patients présentaient des lésions gastriques. L'existence de lésions œsophagiennes n'apparaît pas significative.

2) des lésions gastriques chez 8 patients (dont 7 sont décédés) et l'absence de lésion gastrique chez 1 malade, décédé. L'existence de lésions gastriques, comme l'ont montré Bismuth et Coll., apparaît significative ($p < 0,05$).

Ceci confirme, comme avec tout produit caustique, qu'un bilan endoscopique complet de l'œsophage et de l'estomac est toujours nécessaire, entre la 4ème et la 8ème heure, même en l'absence de lésion haute (bouche, pharynx).

Dans 4 observations, nous avons constaté une apparition retardée des lésions caustiques digestives.

Bismuth et coll.(2), dans leur série, observent des lésions buccales chez tous les malades, alors que nous constatons que ces lésions peuvent être absentes au décours immédiat de l'intoxication et apparaître ensuite. Cette différence peut s'expliquer, hormis les intoxications bénignes non hospitalisées en réanimation, par le délai possible de transfert des patients en réanimation.

Ainsi, la possibilité d'une apparition retardée ou d'une aggravation des lésions démontre leur méconnaissance possible lors du premier bilan endoscopique et la nécessité, semble-t-il, d'un contrôle systématique à la 48ème heure.

TABLEAU I

| Patient | Bilan d'entrée | Evolution |
|---------|--|--|
| I | Pas de lésion buccale fibroscopie : stade I œsophagien | Au 3ème jour : nécrose retardée de la moitié postérieure de la langue Pas de nouvelle fibroscopie Guérison |
| II | Examen ORL normal Fibroscopie : stade I œsophagien | Au 2ème jour : - ulcérations buccales - Fibroscopie : stade II œsogastrique - décès |
| III | Pas de lésion buccale Fibroscopie : normale à la 19ème heure | - bouche : inconnue - au 4ème jour : stade II œsogastrique - décès |
| IV | Examen ORL : œdème laryngé Fibroscopie : œsophage normal, stade I gastrique | - à la 36ème heure : perforation œsophagienne - décès |

8 - Insuffisance rénale organique

Nous avons exclu, dans l'étude de ce critère :

- 3 patients, décédés entre la 11ème et la 36ème heure, dont le bilan rénal était normal à l'entrée, mais l'évolution de la fonction rénale inconnue.
- et 8 patients, dont 5 sont décédés, dont le bilan rénal nous est inconnu.

16 patients ont eu un bilan rénal complet :

- dans 2 cas, d'évolution favorable, le bilan rénal est toujours resté normal.

Insuffisance rénale fonctionnelle : elle est notée chez 4 patients, dont 2 sont décédés. Sur ce trop faible échantillon, nous ne pouvons tirer aucune conclusion sur la valeur pronostique de l'insuffisance rénale fonctionnelle, mais nous savons, comme l'ont montré Bismuth et coll.(2), que l'insuffisance rénale fonctionnelle, est sans valeur pronostique.

Insuffisance rénale organique : 10 malades, tous décédés, présentaient une insuffisance rénale organique. Dans 2 de ces cas, le patient est décédé d'une fibrose pulmonaire avec, au moment du décès, une amélioration de l'insuffisance rénale.

Nous retrouvons une valeur significative à l'insuffisance rénale organique ($p < 0,02$).

9 - Perturbations du bilan hépatique

15 patients ont eu un bilan hépatique. Nous avons exclu de cette étude un patient chez lequel les perturbations du bilan hépatique constatées à l'entrée ont été rapportées à une cirrhose éthylique. Dans 6 cas, dont 3 sont décédés (entre la 20ème et la 31ème heure), le bilan hépatique est resté normal.

8 patients, dont 7 sont décédés, ont présenté une atteinte hépatique, en règle de type cytolitique, apparue dans les 24 premières heures.

Nous ne retrouvons pas de valeur significative à ce critère.

10 - Gazométrie et épreuve fonctionnelle respiratoires

1) Gazométrie

19 patients ont eu une étude des gaz de sang. Nous avons exclu un patient qui présentait à l'entrée une PaO₂ élevée, liée à une oxygénation précoce, avant son arrivée en réanimation, et 4 patients (dont 3 sont décédés) qui n'ont eu qu'une étude de la PaO₂.

Chez 3 patients, tous décédés, la PaO₂ à l'entrée, était inférieure à 10 k Pa ; dans un cas associé à une hypocapnie, dans un cas à une normocapnie et dans un cas à une hypercapnie.

Chez 11 malades, dont 8 sont décédés, la PaO₂ était normale à l'entrée, associée chez 2 patients décédés à une hypocapnie.

2) Epreuves fonctionnelles respiratoires

Elles n'ont été réalisées que chez 3 patients, dont un est décédé d'un collapsus cardio-vasculaire à la 31ème heure et ont toujours été normales.

Cet examen n'a pas été pratiqué dans 24 cas, en raison du décès précoce de certains malades avant sa réalisation, d'une ventilation parfois très tôt instituée pour d'autres, enfin parfois en raison d'une hospitalisation dans un hôpital périphérique ou d'Outre-mer, où il n'a pas été réalisable.

Le manque de renseignements concernant ces 2 examens dans de nombreux dossiers, des dosages gazométriques prélevés à des temps différents et donc difficilement comparables, ne nous permettent pas de conclure sur leur valeur significative. Cependant l'expérimentation animale(10) et certaines observations cliniques bien documentées ont montré l'intérêt de leur étude systématique.

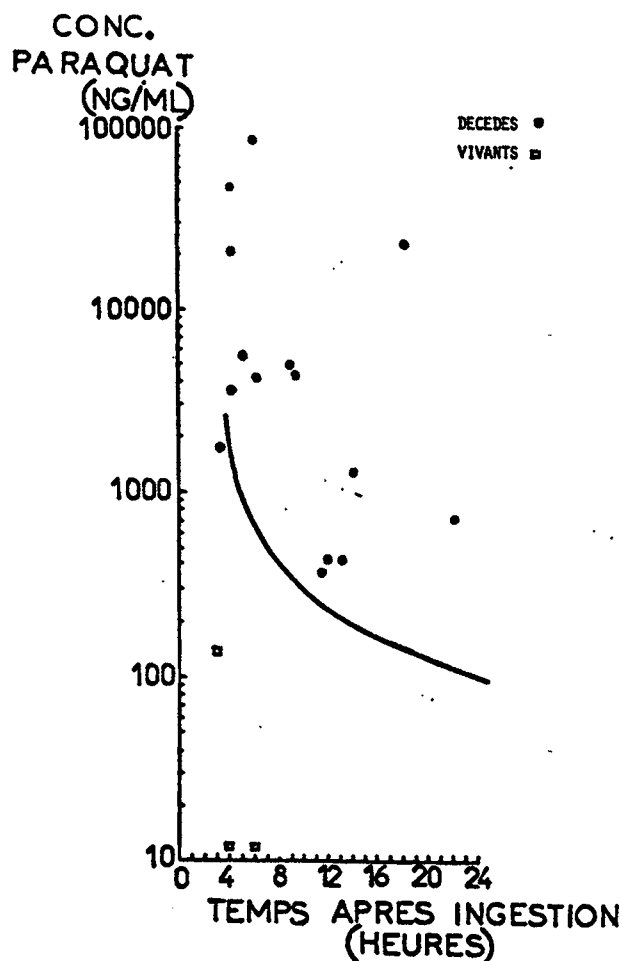
11 - concentration plasmatique de paraquat

L'étude de Proudfoot(15) a montré que les patients qui ont une concentration plasmatique de paraquat supérieure à :

| | |
|-----------|------------------|
| 2 mg/l | à la 4ème heure |
| 0,6 mg/l | à la 6ème heure |
| 0,3 mg/l | à la 10ème heure |
| 0,16 mg/l | à la 16ème heure |
| 0,1 mg/l | à la 24ème heure |

décèdent.

Dans notre étude, le Paraquat sanguin a été dosé dans 23 cas, dont 9 décès. Chez 14 patients, décédés, le taux sanguin se situait au dessus de la courbe. Un seul patient, décédé au 8ème jour d'un collapsus cardio-vasculaire, avait une concentration plasmatique à la 4ème heure inférieure à 2 mg/l ; mais ce dosage, effectué dans un autre laboratoire et non par méthode radio-immunologique, ne nous paraît pas fiable.



Dans 1 cas, d'évolution favorable, le taux sanguin se situait au-dessous de la courbe (0,16 à la 3ème heure) et dans 2 intoxications accidentelles bénignes les taux sanguins étaient négatifs.

Nous retrouvons donc une valeur très significative à ce critère ($p < 10^{-5}$).

Nous constatons que les patients qui avaient, dans les 6 premières heures, un taux supérieur à 10 mg/l sont décédés dans les 48 premières heures, d'un collapsus cardio-vasculaire, quel que soit le lieu d'hospitalisation et le type de traitement mis en route.

Pour 5 patients (dont 4 sont décédés) le dosage plasmatique a été effectué tardivement, mais avant tout traitement, entre la 31ème heure et le 4ème jour. Si on prolonge la courbe de Proudfoot au-delà de la 24ème heure, on constate que les 4 patients décédés se situaient au-delà de la courbe et le malade vivant au-dessous.

Cependant, comme pour Proudfoot, notre échantillon de patients est trop faible actuellement pour qu'on puisse tracer une courbe prédictive au-delà de la 24ème heure.

CONCLUSION

Ainsi, cette étude, sur un échantillon différent de patients, confirme la validité des facteurs pronostiques définis par Bismuth et coll.(2) : voie d'absorption digestive, existence de lésions gastriques, insuffisance rénale organique, concentration plasmatique de paraquat.

Sur cette plus large série, nous avons pu mettre en évidence une plus grande sévérité des intoxications volontaires.

Ces paramètres qui apparaissent significatifs, sont en fait strictement liés à la quantité ingérée.

TABLEAU II

| Facteurs pronostiques significatifs | P |
|---|-------------|
| - voie d'absorption digestive | $< 10^{-5}$ |
| - intoxication volontaire | $< 10^{-5}$ |
| - quantité ingérée (≥ 1 gorgée) | $< 0,05$ |
| - existence de lésions gastriques | $< 0,05$ |
| - insuffisance rénale organique | $< 0,02$ |
| - concentration plasmatique de paraquat | $< 10^{-5}$ |

Nous avons constaté, par ailleurs, la possibilité d'une apparition retardée des lésions caustiques digestives que peut méconnaître le premier bilan endoscopique et qui nécessite, semble-t-il, un contrôle systématique à la 48ème heure.

Enfin, un plus grand échantillon de malades, vus tardivement, permettra d'extrapoler la courbe prédictive de Proudfoot jusqu'au 8ème jour.

BIBLIOGRAPHIE

1. ACKRILL P., HASLETON P.S., RALSTON A.J. - Œsophageal perforation due to paraquat. Brit. Med. J., 1978, 1, 1252-1253.
2. BISMUTH Ch., GARNIER R., DALLY S., SCHERMANN J.M., FOURNIER E. - PROGNOSIS AND TREATMENT OF PARAQUAT POISONING. Review of 28 cases. Clin. Toxicol. (sous presse).

3. CALDERBANK A. - The bipyridilium herbicides. Advances Pest. Contr. Res., 1968, 8, 127-235.
4. CONOLLY M.E., DAVIES D.S., DRAFFAN G.H., BENNETT D.N., DOLLERY C.T. - Clinical experience with paraquat poisoning in clinical aspects of paraquat poisoning. Proceeding of an international meeting held on the 7th october 1975. Manchester - Ed. K. Fletcher Publ. I.C.I., 1977.

5. CONSO F. - Intoxication aiguë par le Paraquat - Expérience des Centres Anti-Poisons Français. Bull. Med. Leg. Toxicol., 1978, 21, 117-120.
6. COOKE N.J., FLENLEY D.C., MATTHEW H. - A paraquat poisoning : serial studies of lung function. Qu. Jl. Med., 1973, 42, 683-692.
7. FAIRSHTER R.D., VAZIRI N.D., SMITH W.P., GLAUSER F.L., WILSON A.F. - Paraquat poisoning : an analytical toxicology study of three cases. Toxicology, 1979, 12, 259-266.
8. FISHER H.K. - Two experiments not previously described - 1 non human - 2 human based on some previous work - in Clinical aspects of Paraquat poisoning : Proceedings of an International Meeting held on the 7th October 1975. Manchester. Ed K Fletcher. Publ Imperial Chemical Industries Limited 1977.
9. GUYON F., BISMUTH Ch., LECLERC J-P., DAUCHY F. - intoxication massive par le Paraquat mortelle en moins de 24 heures - Données toxicologiques et anatomocliniques. Eur. J., Toxicol., 1974, 7, 182-187.
10. LAM H.F., TAKEZAWA J., GUPTA B.N., VAN STEE E.W. - A comparison of the effects of Paraquat and diquat on lung compliance, lung volumes and single breath diffusing capacity in the rat. Toxicology 1950, 18, 111-123.
11. MATTHEW H., WRIGHT N., ROBSON J.S., FLENLEY D., BROWN S.S., HEARD B.F., HOUSLEY E., SWAN A.A.B., KENNEDY W.P.U., DONALD K.W., Mc HARDY G.J.R., PRESCOTT L.F. - Paraquat poisoning : clinicopathological conference. Scot. Med. J., 1971, 16, 407-421.
12. MURRAY R.E., GIBSON J.E. - Lethality and pharmacokinetics of Paraquat in rats. Toxicol. Appl. Pharmacol. 1971, 19, 405.
13. OKONEK S. - Vergiftungen durch Paraquat oder Diquat. Toxikologische befunde und neue therapeutische Möglichkeiten. Med. Welt. 1976, 27, 1401-1404.
14. OKONEK S., SETYADHARMA H., BORCHERT A., KRIENKE E.G. - Activated charcoal is as effective as Fuller's earth or Bentonite in Paraquat poisoning. KLIN. WOCHENSCHR. 1982, 60, 207-210.
15. PASI A., - The toxicology of Paraquat, diquat and morfamquat. Hans Uber Publischers (Bern Stuttgart, Vienne) 1978.
16. PROUDFOOT A.T., STEWART M.S., LEVITT T., WIDDOP B. - Paraquat poisoning : significance of plasma-paraquat concentrations. Lancet, 1979, 2, 330-332.
17. ROSE M.S., PARKINSON G.R., LAIRD W.J.D. - The effect of administration of an emetic (PP 796) on paraquat toxicity in dog and monkey. I.C.I. non publié.
18. SMITH L., WRIGHT A., WYATT I., ROSE M.S. - Effective treatment for Paraquat poisoning in rats and its relevance to the treatment of Paraquat poisoning in man. Br. Med. J., 1974, 4, 569-571.
19. VALE J.A., CROME P., VOLANS G.N., WIDDOP B., GOULDING R. - The treatment of Paraquat poisoning using oral sorbents and charcoal haemoperfusion. Acta Pharmac. Tox., 1977, 41, supp. 2, 109-117.

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B-22. THE PLASMA PARAQUAT CONCENTRATION OF DOGS ADMINISTERED PARAQUAT WITH EMETIC

840 840

M Yamashita, K Nakamura, S Sato, and H Naito
214 Yokomachi Sakuraniura, Ibaraki, Japan

High mortality rate has been reported following paraquat ingestion. In order to reduce the mortality rate, emetic has been added to paraquat, but it still accounts for many deaths by paraquat ingestion. Since the opening of our Poison Control Center in September 1981, 20 patients with paraquat poisoning have been admitted to our poison treatment center. Only 2 patients survived and the mortality rate is 90%. The average dose of paraquat ingested by patients treated in our center was 422 mg/kg, which is much higher than LD₅₀, 30 mg/kg in dogs.

There is a possibility that vomiting does not make much difference in blood concentrations when large doses of paraquat are ingested. Studies were carried out to see the blood concentrations following ingestion of paraquat with or without emetics using two kinds of doses.

METHOD

Twenty-six mongrel dogs weighing 10-15 kg were used. Dogs were given nothing by mouth except water on the day of the experiment. Sedation was produced by 10-15 mg/kg of ketamine intramuscularly. Electrocardiogram was monitored and femoral artery and vein were cannulated for monitoring blood gases and blood sampling. The paraquat used in this experiment was commercial preparation containing 24% paraquat and 0.05% emetic or 25% paraquat in water (Figure 1).

A gastric tube was orally inserted and the stomach contents were aspirated. The 30 mg/kg or 250 mg/kg of paraquat with or without emetics diluted with water to make a total volume of 50 ml was injected into the stomach through the gastric tube. The tube was removed immediately after injection of paraquat and dogs were kept in a frame. Blood samples were drawn 1, 2, and 4 hours after paraquat

Table 1. Plasma concentrations following ingestion of paraquat 30 mg/kg (4 determinations per mean \pm standard deviation).

| Hour | Paraquat (g/ml) | Paraquat + Emetic (g/ml) |
|------|-----------------|--------------------------|
| 1 | 5.4 \pm 1.5 | 2.9 \pm 0.8 |
| 2 | 9.2 \pm 1.4 | 3.2 \pm 1.6 |
| 4 | 5.1 \pm 1.2 | 1.3 \pm 0.5 |

administration. Paraquat concentrations in plasma mean values between two groups was tested using student's t-test.

RESULTS

Severe vomiting started about 15 minutes after administration of paraquat with emetic in both 30 mg/kg and 250 mg/kg. Vomiting usually appeared around 1 hour after administration of paraquat with an emetic in 250 mg/kg dose but no vomiting was noted in dogs given 30 mg/kg of paraquat without emetic. One out of the 9 dogs given 250 mg/kg paraquat without emetics vomited within one hour. Supraventricular arrhythmias were noted in dogs given 250 mg/kg of paraquat with emetic. Arterial blood pH, pO₂, and pCO₂ remained within normal limits in all dogs during the experiment. Paraquat concentrations in blood 1, 2, and 4 hours after administration of 30 mg/kg of paraquat into the stomach are shown in Table 1. Values are expressed as mean \pm standard deviations with numbers of determinations in parenthesis. Blood concentrations after paraquat with emetics are significantly lower than that without emetics. However, when large doses (250 mg/kg) of paraquat were given, there are no difference in blood concentrations between paraquat with and without emetic as seen in Table 2.

Table 2. Plasma concentrations following ingestion of paraquat 250 mg/kg (9 determinations per mean \pm standard deviation).

| Hour | Paraquat (g/ml) | Paraquat + Emetic (g/ml) |
|------|------------------|--------------------------|
| 1 | 112.4 \pm 42.2 | 106.9 \pm 47.0 |
| 2 | 94.6 \pm 50.2 | 89.6 \pm 39.2 |
| 4 | 53.3 \pm 32.3 | 39.1 \pm 22.9 |

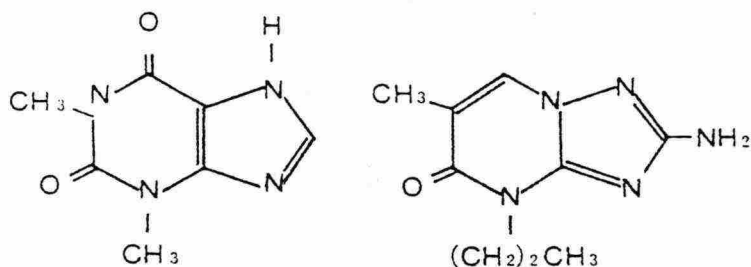


Fig 1 - The structural formulas of theophylline and emetic in paraquat.

DISCUSSION

Since severe vomiting was noted soon after giving paraquat with emetic, quantities of paraquat in the intestine are presumably smaller than that without emetics in both doses. This is reflected in our experiment of 30 mg/kg of paraquat.

However, it is hard to explain that there is no difference in blood concentrations between paraquat with and without emetic when large doses are given. There might be a

possibility that higher doses of emetic in paraquat promote the absorption of paraquat from the intestine. Emetic in paraquat is shown in Figure 1 and is similar in its chemical formula to theophylline. Theophylline is known to increase splanchnic circulation. It is therefore quite likely that a high dose of emetic in paraquat increases splanchnic circulation and thereby intestinal absorption. Supraventricular arrhythmias observed in dogs given 250 mg/kg of paraquat with emetic are also known as a side effect of theophylline.

C. EMERGENCY MEDICAL SERVICE RESPONSE TO TOXICOLOGIC EMERGENCIES

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Each year the American public consumes an estimated 15 billion dollars of health care in almost 5000 emergency departments. Depending on definitions, well over 10% of these visits are for toxicological or pharmacological illnesses. This 1.5 billion in emergency care dollars translates to about 8 million individual instances of human suffering and more annual deaths than those from airplane crashes, bee stings and drownings put together. Providing emergency care 24 hours per day to these patients are 15,000 Emergency Physicians with advice and information from several hundred toxicologists. Regardless of well publicised differences in priorities and techniques, it is shared responsibility to decrease the incidence and severity of all poisoned patients and to use the health care dollars saved for other pressing human needs.

Much has been said and will be said here on treatment modalities. I am not an expert in those fields. You are--and I'm proud to say, many of you are Emergency Physicians. I would like to address pre-hospital care, emergency department care and emphasize prevention--the most effective of all treatment modalities.

Television, magazines and novels all abound with examples of paramedics--those sun-tanned, thin, dextrous machine marvel laden men who see more action in 30 minutes than I see in a week at my emergency department. The concept of taking the hospital to the patient began in this country in the late 1960s and, like anything new in medicine, if some was good, more was better. Some paramedic squads must be staffed by three people just to carry the equipment. No Emergency Medicine is having to face the issue of how much is "Just Right."

All ambulance personnel, regardless of their level of training, should be able to provide some basic services to the poisoned patient. Ipecac should be available on the vehicles and the Emergency Medical Services personnel should be authorized to administer it upon order of a physician. Containers of pills or ingested substances should routinely be found and brought with the patient to the receiving facility. Life support stabilization should be available based on the ambulance personnel's level of training. For Emergency Medical Technicians, this may consist only of Cardio-pulmonary Resuscitation but for paramedics a secure airway and artificial ventilation via an endotracheal tube, intravascular volume expansion and cardiac monitoring may obviate the need for more radical and less effective treatment.

Problem areas exist and help is needed to circumvent or eliminate them. Few jurisdictions will allow EMTs to carry any drug, including Ipecac. Fewer yet will allow them to administer it even on order of a physician. Fears of liability and resistance to change are problems at present not yet overcome. The result is delayed stomach emptying, increased potential for toxicity, and an expensive trip and visit to an emergency department.

Some training programs, including those sponsored by national medical groups, fail to emphasize or mention to the future EMT or paramedic the importance of bringing into the emergency department containers of ingested substances. "Oh, it was Ajax Bowl Cleaner." Valuable information such as "Lemon-Fresh? Spray? Liquid? How much?" goes unanswered. These personnel must be better trained in such simple procedures and that is primarily Emergency

Mitchell Julie JA

From: Davis Martin MT
Sent: 08 October 1997 11:10
To: Mitchell Julie JA
Cc: Scott Bob RC - CTL
Subject: ID PQ Threat to Registration
Sensitivity: Private

Dear Julie,

Thanks for talking with me earlier. Today's issue arises from Paraquat Poisoning Mechanisms* Prevention*Treatment edited by Chantal Bismuth & Alan H. Hall Chapter 10 which has come into the hands of Kasumbogo Untung of DoE Indonesia.

Untung and others are fighting to the last to reverse the impending Ministerial Decree which could improve the situation of our paraquat registration.

Specifically, Untung is targeting peat soils (not your prob) and the emetic.

May I quote from this work?

Since January 1978, some paraquat formulations contain an emetic that raised the LD50 of paraquat fivefold in monkeys. However, it is not certain that the addition of the emetic improves the prognosis in cases of human paraquat ingestion. Published case series do not permit this conclusion (13 = J.H. Frelon, P.Merigot, R.Garnier, C.Bismuth and M.L. Efthymiou. Facteurs pronostique de l'intoxication aigue par le paraquat. Etude retrospective des cas enregistrés au Centre Anti-Poisons de Paris en 1981, Toxicol. Eur. Res., 5: 163 (1983). Moreover, a recent study in dogs indicates that the emetic additive does not cause early vomiting, and that it may actually increase the systemic absorption of pq from the G.I. tract (36 = M. Yamashita, K. Nakamura, S. Sato and H. Naaito. The plasma pq concentration of dogs administered pq with emetic, Vet. Hum. Toxicol., Suppl.448(1982). The chemical composition of the emetic is similar to theophylline, raising the possibility that the emetic itself might have neurotoxicological and cardiovascular toxicity.

Now, I have at the back of my mind that the data from the Paris Poison Centre was based on a small population which included a high - if not total - incidence of deliberate ingestion. Data from accidental ingestion was a small %age of the population.

18 Deliberate / 9 accidental.

41 cases but only 27 used in analyses

Similarly, I am minded that the Japanese work was ill-defined and that the experimental design was wanting. Methodology used to assess plasma concentrations was possibly suspect.

Furthermore, I'm not sure if the reference to monkeys relates to PP796 or not.

These are my thoughts but I would be grateful for yours and Bob's support because I need to respond to Untung hard and factual if we are to rescue our situation.

I am copying this to Martin Wlks because I know that Jaakrta have contacted him directly but he is unobtainable today and I would be most grateful for the earliest support for my interpretation or otherwise.

Thanks & Regards

Martin

*of 18 Deliberate - All Died - cardiovascular/renal/pulmonary
2/9 Accidentals died - pulmonary.
This study estimates adult LD of 70kg of 35mg/kg.*

*= 2450mg
~ 70kg.
= 2.45g.*

ACIDOSIS AND DEATH. Zolet DI, Miller T, Yarborough B and Garrettson LK; Richmond, Virginia, USA.

Three cases of pentaborane (B5H9) poisoning occurred during the destruction of cylinders of unknown gases. Assay of the offending gas by gas chromatograph-mass spectrograph showed B5H9 only. Within 15-20 min of exposure all had respiratory irritation and within 15-45 min all convulsed. After general tonic-clonic convulsions, the fatally poisoned patient exhibited two opisthontonic convulsions and no further spontaneous neurologic function. In the emergency department, blood pH was 6.4 in 2 pts with bicarbonate of 5 mEq/l. In one, pH was 7.0 and lactate was 22 mEq/l. BP required support in two, as did ventilation. All had elevations of SGPT greater than SGOT and all had rhabdomyolysis with CPK in one rising to 47,000. Neutrocytosis lasted 1 week and lymphopenia lasted 2 weeks. One died; one remains unconscious after 2.5 weeks. Exposure was primarily by inhalation, but dermal absorption may have occurred. Ten of 11 EMT's involved were hospitalized with a less severe illness.

B-17 HYDROFLUORIC ACID: A NEW CORROSIVE POISON? Jordan J and Dean BS; Pittsburgh Poison Center, Pittsburgh, Pennsylvania, USA.

Hydrofluoric acid has long been recognized as a serious industrial hazard. Commercially it is used in brick stone and aluminum cleaners, but rarely in concentrations greater than 20%. The health care professional, unaware that hydrofluoric acid is available on the consumer market, may mistakenly assume that he/she is treating hydrochloric acid. The toxicity of hydrofluoric acid, like all mineral acid, is principally due to corrosive action. However, it also releases its fluoride ion in the deep tissue layers. Solutions of less than 20% may cause a burn which manifests itself with pain, erythema and a latent period up to 24 hours. Lack of positive clinical symptomatology and incorrect acid identification were two obstacles encountered by the Pittsburgh Poison Center. The discussion will include three cases differing in patient age, acid concentration, duration of exposure, medical management provided, and length of disability.

B-18 TRICHLORETHYLENE TRIGEMINAL NEUROPATHY. A NEW DIAGNOSTIC APPROACH: THE EVOKED POTENTIAL. Barret L, Garrel S, Arsac PH, Debru JL and Faure J, Cedex, France.

Authors present a study concerning Trichlorethylene Trigeminal nerve impairment. Study is conducted among workers occupationally exposed (40 cases). Authors propose a new exploration method which consists in recording somato sensory evoked potential following stimulation of this nerve. Results are correlated with clinical findings and exposition parameters. They confirm this elective neurological disturbance. Particular character of the observed anomalies opens a debate about Trichlorethylene neurotoxicity mechanism. Routine use of this method is discussed as a prevention mean in Trichlorethylene chronic exposure.

B-19 EPIDEMIOLOGICAL AND TOXICOLOGICAL FACTORS ASSOCIATED WITH EXPOSURE TO CHLORINATED DIBENZOFURANS IN MAN AND ANIMALS. Cordle F; Washington, USA.

Chlorinated dibenzofurans have been identified in a number of chemical products, in particular the polychlorinated biphenyls (PCBs). Studies in a variety of animal species have indicated that

the dibenzofurans may be more toxic than the primary compounds. The potential human consequences of exposure to the dibenzofurans has been reported from Japan where exposure occurred as the result of the consumption of rice oil (Yusho). This paper will review the epidemiology and toxicology of exposure to the dibenzofurans. 840

B-20 EVOLUTION OF COMA IN CHILDREN WITH CHLORINATED INSECTICIDES INTOXICATION TREATED WITH PIRACETAM. Schwartsman S; Sao Paulo, Brazil.

Two series of cases of chlorinated intoxication in children in comparable age, sex, nutritional status, depth of coma, and having had at least one convulsive crisis, were studied. In the first series the children were submitted to the standard treatment (control of seizures, respiratory care, and fluid and electrolyte balance maintenance). In the second series it was added piracetam to the treatment, 50 mg/kg IV each 8 hours. The outcome of coma, based on Dechaume and Jouvett's modified score, was more successful in the second group, and this was associated to a smaller frequency and severity of convulsive disorders, and neurological symptoms post-coma.

B-21 PARAQUAT REMOVAL BY HEMOPERFUSION UTILIZING A BEADED COMPOSITE SORBENT. Tabak A, Lotan N, Sideman S, Taitelman U, Mihich M and Lupovich S; Haifa, Israel.

The study deals with the performance of a column which is used for paraquat detoxification by hemoperfusion. The system is based on a newly developed sorbent material made of Fuller's Earth powder encapsulated in crosslinked agarose beads (Talosit). The crosslinking of the agarose by epichlorohydrin greatly increases the mechanical strength of the beads, and enables their sterilization in the autoclave. No significant changes in plasma composition had taken place when the beads were properly conditioned prior to their contact with fresh human blood. In vitro and in vivo paraquat removal rates by the new beads compare favorably with cellulose coated activated charcoal. The results obtained so far by hemoperfusion of rats and dogs with this new sorbent are very promising, and work is continuing to ascertain the biocompatibility characteristics of the new system.

B-22 THE PLASMA PARAQUAT CONCENTRATION OF DOGS ADMINISTERED PARAQUAT WITH EMETIC. Yamashita M, Nakamura K, Sato S and Naito H; Ibaraki, Japan.

In 1975, the addition of the emetic agent to paraquat was carried out as a possible way of reducing the toxicity. Many deaths from paraquat poisoning in man has occurred in spite of the strong vomiting after the ingestion. This study was undertaken to investigate the plasma concentration after oral administration of paraquat with emetic in dogs. Method: Mongorel dogs weighing 8-10 kg were sedated with 10 mg/kg of ketamine intramuscularly. A stomach tube inserted via the esophagus. After stomach was aspirated, dogs were dosed by stomach tube with 30 or 250 mg/kg of paraquat either with or without emetic. Blood samples were taken from the femoral vein 1, 2 and 4 hours after paraquat administration. Results: All dogs dosed with paraquat with emetic vomited. The concentration of paraquat in the plasma of dogs dosed with 30 mg/kg of paraquat with emetic was considerably less than that without emetic. However, when dogs were dosed with 250 mg/kg of paraquat, any difference was not observed in the plasma concentration of paraquat either with or without emetic. 270

Yamashita / Nakamura.
Vet Hum Tox Suppl 48 1982.

Dogs. Commercial Prep. — 24% Pp.
0.05% Enetic.

30mg/kg (+ Enetic.
or 250mg/kg)

↓
Diluted in 50ml H₂O

↓
Intragastric tube.

| | Vomit | Time to vomit |
|------------|------------|---------------|
| 30mg/kg + | Severe (*) | 15 mins. |
| 30mg/kg - | No Vom | — |
| 250mg/kg + | Severe | 15 mins |
| 250mg/kg - | 1/9 Vom. | Within 1 hr. |

(*) Also said That 30mg/kg + Enetic /
dose group vomited within 1 hr.

Speculate that enetic ~~is~~ (higher doses)
may promote Pp absorption from intestine —
bases on enetic's structural similarity to
Theophylline — which is known to increase
splanchnic circulation!

41 Cases. - 1981. - Poison Control Centre, Paris

Apparently saying that enetic doesn't work,
ie doesn't increase survival.

② Yamashita / Naramura. ~~JEV~~ Vet Hum Tox
Pp/Dog. Suppl. 48. 1982.

Enetic doesn't cause early vomit.

Evidence to suggest that ~~it~~ enetic
causes increased absorption of Pp.

③ Bismuthard Hau. Pp Poisoning. ~
Monographs. - Enetic no good
- ↑ absorption of Pp
etc...

Indonesians are spouting these data/
sources. Zeneed need a position
document on their validity etc...
by this pm.

Martin Davies sending thro' more detail.

Flebon - et al.

Their experience shows that

if take less than 1 monthful. \rightarrow 25% mont.
 \geq 1 monthful. \rightarrow 84.2% mont.
 $>$ " \rightarrow 100% mont.

Conc of PQ in this study.

| | | |
|----------------|---------|--------------|
| 23. (19 dead). | 20% PQ. | Concentrée ? |
| 2. (1 dead) | 12% PQ. | " |
| 2 survivors. | 20% PQ | Diluée |

Presence of Genetic

ZENECA

Central Toxicology Laboratory

Alderley Park
Macclesfield
Cheshire SK10 4TJ
England

Telephone 01625 582711
Telex 669095/669388 ZENPHA G
Fax 01625 585715

Fax Cover Sheet

FROM: Helen Royce
Company Name: RAD Fernhurst
Fax Number: Redacted - EU PII
TO: Rob Scott
Date: 9/10/97 Time: 11 am
Number of pages following cover note: 20

Cover Note:

Copies as discussed - from Rob Scott a Dr Locke
(re paraquat)

Many thanks
as Andy gave me
all clear to send
them all onto
Nigeria
Helen

CABINET/ _____
DRAWER/ _____
PC / _____
INITIALS/ _____

RECEIVED
RAD
- 9 OCT 1997

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Central Toxicology Laboratory is the
UK agent for Zeneca Limited.
Registered in England No 2710945
Provisional Office
15 Stanmore Gate
London W11 4LN

Carol

DRAFT.

Effect of Addition of Emetic to
Pipiforms. on Acute Poisoning
in man. Hunt TB, Whitehead A
I2235B. 1984.

TABLE 1

MORTALITY OF NON-EMETIC PARAQUAT POISONING

| | Fatal | Non-Fatal | % Mortality |
|----------------------------|-------|-----------|-------------|
| <u>Solid Formulations</u> | | | |
| Weedol | 38 | 131 | 22.5) |
| Pathclear | 1 | 11 | 8.3) 21.5 |
| <u>Liquid Formulations</u> | | | |
| Gramoxone | 119 | 18 | 87) |
| Dextrone | 4 | 5 | 44) 84 |

TABLE 2

MORTALITY OF EMETIC PARAQUAT FORMULATIONS

| | Fatal | Non-Fatal | % Mortality |
|----------------------------|-------|-----------|-------------|
| <u>Solid Formulations</u> | | | |
| Weedol | 14 | 116 | 11) |
| Pathclear | 5 | 25 | 17) 12 |
| <u>Liquid Formulations</u> | | | |
| Gramoxone | 40 | 20 | 67) |
| Dextrone | 1 | 3 | 25) 64 |

TABLE 3

POTENTIAL LETHAL ORAL DOSE OF PARAQUAT (HUMAN)

| Dose of Paraquat Ion Reported as being Swallowed | No Fatal | No Non-Fatal | % Mortality |
|--|-------------|-----------------|-------------|
| <2 g | 10 | 93 | 9 |
| 3 to <5 g | 29 | 23 | 56 |
| 5 to <10g | 18 | 2 | 90 |
| 10g or more | 43 | 0 | 100 |

Scott Bob RC - CTL

From: Heylings Jon JR
Sent: 04 September 1997 13:15
To: Scott Bob RC - CTL
Cc: Ishmael John J; Atherton Keith KT
Subject: FW: PP796
Importance: High

Bob,

As the attached note was circulated to me, I would like to be involved in the response back to the business on the effectiveness of the emetic.

I discussed this with John Ishmael yesterday and this may be a relevant topic to bring to the attention of the bipyridyl project team.

I think, like the paraquat poisonings issue, that we should all agree a single CTL view on these important topics.

Jon

From: Cook Andy AR (ALL-IN-1)
Sent: 08 August 1997 12:26
To: Scott Bob RC (ALL-IN-1)
Cc: Heylings Jon JR@EXCHNG; Wilks Martin MF (ALL-IN-1)
Subject: PARAQUAT: PP796
Importance: Low

Bob,

Could you please provide me with a short (c. 1/2 page for each of the criteria listed below) document for use opposite regulators (mostly in LDCs) which clearly establishes that PP796 fulfils the criteria given below:

- It must be rapidly absorbed (more rapidly than paraquat) and be quick acting. ✓
Emesis must occur in about half an hour in at least 50% of cases.

- It must be an effective (strong) stimulant of the emetic centre to produce effective emesis. The emetic effect should have a limited 'action period' of about two to three hours to allow effective treatment of poisoning. ✓

- It must act centrally on the emetic centre in the brain. ✓

- It must not be a gastric irritant because, as paraquat itself is an irritant, this could potentiate the toxicity of paraquat. ?

- It must be toxicologically acceptable. It must have a short half-life in the body (to comply with the need for a limited action period).

- It must be compatible with and stable in the paraquat formulation and not affect the herbicidal efficiency or occupational use of the product.

Wherever possible we should refer to published or independent sources in support of the statements we make.

The new FAO specification lists these criteria for an 'effective emetic' (paraquat dichloride technical concentrate must now contain an 'effective emetic'), the criteria were drawn up on the basis of inputs previously provided by Saba.

The document would need to be available in its final form by Friday 5th September for use with Nigerian regulators visiting the UK (including CTL)

*no data Toxicol Toxrep
STN.*

*This amount
would be present
in 15ml 200/16
PP 1 on form 2.*

*m.d. 40mg/kg
on 3000mg
in 70kg man.*

week beginning 8th September.

Thanks in advance for your assistance.

ANDY

From: Andy Cook
COOK AR0A1@FHVAXC

Date: 25-Jul-1997 10:07

TO: Bob Scott - CTL
CC: Heylings Jon JR@EXCHNG
CC: Martin Wilks

(SCOTT RC @ A1 @ APVXC1)
(6=Heylings07=Jon08=JR04=CTL03=ZENECA0X400
(WILKS MF0A1@FHVAXC)

Subject: PARAQUAT: PP796

Bob,

Could you please provide me with a short (c. 1/2 page for each of the criteria listed below) document for use opposite regulators (mostly in LDCs) which clearly establishes that PP796 fulfils the criteria given below:

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- It must be an effective (strong) stimulant of the emetic centre to produce effective emesis. The emetic effect should have a limited 'action period' of about two to three hours to allow effective treatment of poisoning.
- It must act centrally on the emetic centre in the brain.
- It must not be a gastric irritant because, as paraquat itself is an irritant, this could potentiate the toxicity of paraquat.
- It must be toxicologically acceptable. It must have a short half-life in the body (to comply with the need for a limited action period).
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Wherever possible we should refer to published or independent sources in support of the statements we make.

The new FAO specification lists these criteria for an 'effective emetic' (paraquat dichloride technical concentrate must now contain an 'effective emetic'), the criteria were drawn up on the basis of inputs previously provided by Saba.

The document would need to be available in its final form by Friday 5th September for use with Nigerian regulators visiting the UK (including CTL) week beginning 8th September.

Thanks in advance for your assistance.

ANDY

*Julie : please progress as far as you can.
Let's discuss we have some time !
Bd*

280

Paraquat
Nigeria
GeneralGeneral
Nigeria

25.6.97

*

INTEROFFICE MEMORANDUM

Date: 25-Jun-1997 03:22pm BST
From: Helen Royce
ROYCE HM
Dept: R/A
Tel No: [redacted]

TO: Andy Cook

(COOK AR)

CC: Martin Davis

(DAVIS MT)

Subject: FAO paraquat specs. - statement from Z

Has anyone asked you if Zeneca would produce some sort of TO WHOM IT MAY CONCERN letter saying that Zeneca's emetic/GRAMOXONE confirms to all the criteria laid down by FAO. The reason I ask is because we are having trouble with pq in Nigeria at the moment, where it is waivering towards a ban, and currently a big tender has come up from the oilfields where we want to submit GRAMOXONE - big bucks if we get it. Mark Spinney is out in Nigeria at the moment and he took the FAO specs with him. Both Mark and Chris Waller think that we might also need to produce further documentation to say that only our emetic confirms to the criteria etc. However we will only submit this if we are specifically requested to do so, therefore we should have it up our sleeve to send at a moment's notice if it is needed - within the next 3 weeks.

Chris has had some contact in the past with John Ismael from CTL on safeners and suggests that he might be the best person to approach.

What I am asking is firstly have you already got some documentation that I could use, if not, do you have any objections if I approach John Ismael and thirdly would John be the best person to ask anyway.

Any thoughts, suggestions, comments?

Helen

PP796: ACUTE ORAL TOXICITY TO THE RAT

1. INTRODUCTION

A sample of PP796 (batch reference BX564) was sent to this Laboratory for assessment of its acute oral toxicity. The work was done during February 1988.

2. SUMMARY OF RESULTS

Moderate signs of toxicity were seen following a dose of 100mg/kg. All animals survived at this dose level. Marked signs of toxicity were seen at both 150mg/kg and 200mg/kg, with nine out of ten animals dosed with 150mg/kg and eight out of ten dosed with 200mg/kg being found dead or killed in extremis by Day 2. The acute oral median lethal dose was estimated as being between 100-150mg/kg.

3. METHODS AND RESULTS

3.1 Acute Oral Toxicity

CTL Study No: AR4583

Groups of five male and five female Alderley Park SPF albino rats were used, bodyweight range 230-304g for males and 175-217g for females. The animals were fasted for a period of up to 24 hours immediately prior to dosing. Preparations of the test sample, in polysorbate 80, were then dosed at a standard volume of 10ml/kg. On Day 1 single doses of 100, 150 and 200mg/kg were administered by stomach tube to separate groups of animals. The animals were observed daily until the end of the study (Day 15). Animals killed in extremis and those surviving until the end of the study were humanely killed by inhalation of excessive levels of halothane BP

followed by cervical dislocation and were examined by necropsy for any macroscopic abnormalities. The acute oral median lethal dose was estimated from the mortality data.

Moderate signs of toxicity were observed at 100mg/kg. All animals had recovered by day 7. Three male and two female rats were killed in extremis and one male and two female rats were found dead on days 1 and 2 at 200mg/kg. Three male and four female rats were killed in extremis and one male and one female rat were found dead on days 1 and 2 at 150mg/kg. Marked signs of toxicity were observed at both these levels. All surviving animals had recovered by day 10.

The most common signs observed at each level included decreased activity, salivation, upward curvature of the spine, increased breathing rate, ptosis and stains around the mouth and nose (see Table 1).

Initially all animals showed a decrease in bodyweight (due to fasting prior to dosing). By day 8 all but one of the surviving animals had increased in weight compared with the initial bodyweight (Day-1) and continued to do so until the end of the study. No macroscopic abnormalities were seen at necropsy.

S L Allen
(Study Director)

.....SLA..... 3 MAY 88

V M Davison
(Author)

.....V.M. Davison..... 27/4/88..

SUMMARY

ICI 63,197 caused slight irritation to rat skin and some evidence of dermal toxicity following repeated occluded application. It caused slight irritation to the rabbit eye on instillation. It was not a strong sensitiser of guinea pig skin. Analysis showed that 0.49% of the particles were within the respirable range.

PROBABLE EFFECTS IN MAN

This material may be of slight systemic toxicity by the dermal route although contact with the skin should not cause significant problems of irritation and sensitisation. Splashes in the eye may cause initial discomfort but only slight transient irritation. If inhaled, a significant amount of the dust could be deposited in the nasal passages and could constitute an emetic dose if absorbed sufficiently.

RECOMMENDED HANDLING PRECAUTIONS

Skin and eye protection should be employed when handling this chemical and any splashes in the eye should be washed away with water. Suitable ventilation or personal protection should be employed to prevent inhalation of the dust.

CTL/T/1277.

PQ Emetic.

EC COUNCIL DIRECTIVE OF 15 JULY 1991 CONCERNING
OF PLANT PROTECTION PRODUCTS ON THE MAF

LEVEL 2 SUMMARY FOR
PARAQUAT

Effect of the Emetic PP796 in Dogs

R C SCOTT

R C Scott
Product Toxicologist

.....

Date

.....

Ref: A:\paraquat.dog
1 March 1995

EC COUNCIL DIRECTIVE OF 15 JULY 1991 CONCERNING THE PLACING
OF PLANT PROTECTION PRODUCTS ON THE MARKET

LEVEL 2 SUMMARY FOR
PARAQUAT

Effect of the Emetic PP796 in Dogs

R C SCOTT

R C Scott
Product Toxicologist

.....

Date

.....

Ref: A:\paraquat.dog
1 March 1995

EC COUNCIL DIRECTIVE OF 15 JULY 1991 CONCERNING THE PLACING
OF PLANT PROTECTION PRODUCTS ON THE MARKET

LEVEL 2 SUMMARY FOR PARAQUAT

R C SCOTT

Effect of the Emetic PP796 in Dogs

The effectiveness of different doses of the emetic PP796 has been assessed in dogs given a simultaneous oral dose of paraquat.

Dogs were given an oral dose of paraquat (20mg/kg) with 0, 0.5, 3.0 or 20mg/kg of PP796. Paraquat peak plasma levels, area under the plasma concentration/time curve and the severity of lung lesions markedly decreased with doses of 0.5 or 3.0mg/kg PP796. These reductions were dose related. The response at 20mg/kg PP796 was variable with some dogs showing reduced effects from paraquat whilst others showed no decrease.

The effective range of the emetic PP796 was between 0.5 and 3.0mg/kg.

Reference

Robinson M and Brammer A (1986). PP796: Emetic Study in Paraquat Treated Dogs. Central Toxicology Laboratory Report Number CTL/T/2471.

EC SUMMARY : LEVEL 2 (emetic PP796 in dogs)

From: Martin Wilks
WILKS MF@A1@FHVAXC

Date: 18-Oct-1994 16:31

TO: Andy Cook
CC: Jane Hall
CC: Bob Scott - CTL

(COOK AR@A1@FHVAXC)
(HALL J@A1@FHVAXC)
(SCOTT RC @ A1 @ APVXC1)

Subject: RE: GERMANY : EMETIC ISSUES

Andy,

thank you for firmly putting the ball in my court. However, I have no intention of letting the other players off the hook that easily. I'm afraid this has to be something of a team effort and we may even have to meet at some stage before your deadline to agree proceedings.

First things first. At our meeting on 31 March 1994 we agreed that

- a) there was no case to take out the emetic, and
- b) there was no evidence that an increased concentration of emetic would lead to a 'safer' paraquat information.

If I remember correctly the second point related to the fact that in a typical suicide scenario the amount of paraquat ingested is often far too high to be sufficiently lowered by the induction of emesis.

It would be useful if we all agreed that these decisions still stand.

With reference to the two specific questions that you are being asked by the German authorities, may I take them in reverse order.

1. Toxicological expert opinion on the effectiveness of the emetic

The appendix to your note provides a good starting point. As I see it, we need essentially an updated version of the Mike Rose document from 1976 (CTL/R/390) which includes studies that have been carried out since (if any). I believe that this should come from CTL (the toxicological experts!), ie. Bob Scott (any objections?).

2. Can the emetic prevent intoxication

This is by far the more difficult question to answer, and all I can do at this point in time is to sketch out my ideas. They go along those lines:

Fact: We know the emetic works in humans (original volunteer/patient data).

Fact: We know that the emetic works in practice ie. vomiting is more frequent and starts earlier with emetic formulations (Bramley & Hart 1983, Meredith & Vale 1987).

Fact: We know that the emetic makes no difference when large doses of paraquat are ingested (>10g, 15g, 20g?).

Fact: When small (accidental?) doses (<1g?) are ingested patients survive with or without emetic.

Question: Does the emetic influence survival in those patients who have

From: Martin Wilks
WILKS MF@A1@FHVAXC

Date: 22-Nov-1994 15:56

TO: Andy Cook (COOK AR@A1@FHVAXC)
TO: Bob Scott - CTL (SCOTT RC @ A1 @ APVXC1)
TO: N.N. Sabapathy (SABAPATHY NN@A1@FHVAXC)

Subject: Paraquat - Emetic - Germany

ACTIONS AGREED AT THE MEETING ON 22 NOVEMBER 1994

ARC to provide original German text of questions asked to MFW.

First-line defence strategy:

MFW to provide answer to first question with help from NNS. Emphasis on overall reduction in accidental poisonings, emetic as part of a package of measures.

RCS to answer second question with help from ARC. Based on ARC's document (attachment to document 16 Oct 1994).

These actions to be completed by mid-December 1994.

Second-line defence strategy:

RCS to draft expert document on animal studies to support inclusion of emetic, including discussion of dose-setting. MFW to supplement with human experience of effectiveness (ie. induction of vomiting).

This action to be completed during first quarter 1995.

MFW 22/11/94

ingested 'moderate' doses (eg. 1-5g)? Do we have good quality data to support our conclusion?

I am looking here specifically to Saba and Andy to comment. Any data, either published, or reported, or in someones filing cabinet, would be particularly appreciated.

While supporting Andy's wish to make the best case possible I believe the first step should be to take stock of what we know.

Any initial comments on whether you support my views or whether I have got the wrong end of the stick are welcome. I will speak to you individually, and perhaps Andy could organise a meeting after 14 November to pull together what we have.

Best regards

Martin

From: Andy Cook
COOK AR@A1@FHVAXC

Date: 11-Feb-1995 10:48

TO: Bob Scott - CTL

(SCOTT RC @ A1 @ APVXC1)

Subject: Document M-II (Tier II), Section 3

Bob,

Thanks for the genotox. text received yesterday afternoon.

I attach the current (WPS-Plus) draft of paraquat Annex II, Tier II (plus reference list) for review. Please return all comments to me by Friday 17th February.

Specific areas which require improvement include the text re. the lack of relevance of the dog NOAEL's for the assessment of risk to man [both operator risk (AOEL) and consumer risk (ADI)]. I still need from you a copy of the Kenneally PhD for submission plus the 'definitive' values for Kmax and Vmaxm to be used in our submission.

The other major subject areas not addressed in the current document are the emetic (against which yourself and Martin have an outstanding action opposite the 'exam questions' from Germany, desklink record of November meeting attached) and the current incidence of accidental vs suicidal fatalities (which I intend to address in the first instance with subsequent review by yourself and Martin).

Also required (asap please and not later than mid-March) are the protocols for all of the agreed paraquat metabolism studies which we are obliged to include in our submission.

All of the above issues are now urgent as the EU submission for paraquat is scheduled for mid-April, all the above requires completion not later than the end of the first week of March.

Thanks.

ANDY

From: Andy Cook
COOK AR@A1@FHVAXC

Date: 16-Oct-1994 17:07

TO: Martin Wilks
CC: Jane Hall
CC: Bob Scott - CTL

(WILKS MF@A1@FHVAXC)
(HALL J@A1@FHVAXC)
(SCOTT RC @ A1 @ APVXC1)

Subject: GERMANY : EMETIC ISSUES

Dear Martin,

In response to an application for 'minor outlet' label extensions in Germany (use in carrots, onions, leeks and parsley) the German regulatory authorities have recently asked us to provide them with the following information :

to D/1 No. 2: submission of information on the question, in how far the emetic PP796 limits the absorption of paraquat and whether an intoxication can therefore be prevented. *Animal vs. man.*

to D/1 No. 2: A toxicological expert opinion on the effectiveness of the emetic and the speed of the start of a vomitus after uptake of PP796 in comparison to other known emetics.

This is not particularly urgent at present but I would be grateful if you could prepare a suitable draft response by Friday 25th November.

I realise that the data we have which relates to the first of these questions is not entirely favourable (for cases of deliberate oral ingestion) however if we can persuade the German authorities of the value of PP796 in advance of the EU review process then this may well prove decisive in determining whether or not we are able to make the inclusion of a suitable pharmacologically active emetic (i.e. PP796) mandatory in all paraquat formulations to be marketed within the EU via the Annex I ('positive listing') process. As such I believe that our response should represent the best case we are able to assemble on the value of the emetic within the EU.

You may find the following text of some help in addressing these questions. I originally compiled this some time ago in order to address similar enquiries which arose from the BGA however in the event this response was never submitted in Germany. Looking at the text now I believe it can be significantly improved on through inclusion of the UK poisoning incident statistics (ODM50, AC/RB, OCT 1992) and the Japanese papers on the occurrence of emesis in patients swallowing paraquat formulations together with a list of references to internal (ICI/ZENECA) study reports and literature publications. Also by placing greater emphasis on the role played by the combination of formulation safety measures (i.e. dye, stench and emetic) in reducing the incidence of cases of accidental ingestion/fatalities.

Please let me know if you need anything further from me.

Many thanks in advance.

ANDY

'TO WHOM IT MAY CONCERN

PP796 EMETIC

In considering the properties of PP796 in comparison with other emetics it is necessary to first consider the criteria which an emetic must meet in order to be appropriate for inclusion in paraquat formulations.

1. Speed and mode of action

The emetic must produce a rapid vomiting response prior to the absorption of toxic amounts of paraquat. It should act centrally and should not produce its action via an irritant effect on the gastric system; irritancy could facilitate the absorption of paraquat.

2. Specificity

The agent must be able to act in the presence of paraquat, i.e. appropriate animal experiments must provide evidence that paraquat does not interfere with the action of the emetic.

3. Human safety

The emetic should be toxicologically acceptable and harmless to the user of the product in which it is incorporated.

4. Environmental safety

The emetic should not have a harmful effect on the environment.

5. Stability

The emetic must be stable in the presence of paraquat and vice versa. The emetic should not interfere with the herbicidal properties of paraquat.

An assessment was made of the following candidate emetic agents, most of which were excluded on the basis that they did not meet one or more of the necessary criteria.

1. Matricaria

This is the ground flower heads of the chamomile plant. It is irritant in action, unreliable and, being insoluble in water, would be of no practical value for use in paraquat formulations.

2. Mustard

This is also highly irritant and insoluble.

3. Salts of heavy metals (eg. copper, antimony and zinc)

These agents are firmly rejected by modern medical opinion because of their high toxic risk. They would also be unacceptable from an environmental perspective.

4. Sodium chloride

This emetic, commonly used in domestic poisoning incidents, is no longer generally recommended by the medical profession. Its efficacy is variable and a number of deaths have occurred following its use.

5. Apomorphine

This agent, although highly effective, can only be administered by intramuscular injection. It is unstable in air. It is therefore clearly of no practical value for inclusion in paraquat formulations.

6. Ipecacuanha

This agent is widely used as an orally administered emetic, it acts on the central nervous system but is also a gastric irritant. When administered in excessive amounts (approximately 10 x the emetic dose) fatalities have occurred. This emetic was seriously considered by ICI for inclusion in paraquat formulations but a study in cynomolgus monkeys found that the response was unpredictable and only effective at doses associated with toxic symptoms.

7. PP796

PP796 is rapidly absorbed in mammals following oral ingestion, peak plasma levels being observed in man during the first hour after administration. In species which vomit such as pig, dog, monkey and man (rodent species do not vomit) the rise in plasma level is associated with the onset of vomiting. This generally occurs within 15 minutes of dosing. Vomiting may be repeated four or five times within the first hour. Thereafter the effect ceases, probably as a consequence of the rapid metabolism and excretion of the compound. The evidence for the action of PP796 being centrally mediated is provided by 1) the rapid onset of vomiting and absence of irritant effects and 2) the production of vomiting in dogs following intravenous administration at plasma levels similar to those producing the effect after oral administration.

PP796 is an extremely potent oral emetic, with man particularly sensitive to its action. A dose of only 0.1 mg/kg is sufficient to produce a 75% expectancy of vomiting in man. Furthermore investigations in monkeys have demonstrated that the induction of vomiting by PP796 is unaffected by the presence of paraquat.

In clinical studies emesis occurred at doses in the range 0.03-0.11 mg PP796/kg (equivalent to 2-8 mg for a 70 kg man). Statistics of paraquat poisoning incidents indicate that most have involved the ingestion of more than 20 ml 'Gramoxone'. Inclusion of PP796 at a rate of 0.05% (5 mg in 10 ml or 0.5 g in 1 litre) is therefore likely to cause vomiting in those ingesting this quantity or above.

In addition to its action as an emetic PP796 has a second property which makes it particularly suitable for inclusion in paraquat formulations as a safening agent. PP796 has been shown to have a delaying effect on gastric emptying, since most paraquat swallowed is absorbed from the small intestine the resulting inhibition of absorption may make a useful contribution in the period immediately following ingestion.

Thus the question of the effectiveness of PP796 in comparison with other emetics is more an issue of which emetics are able to meet the exacting characteristics required rather than a straightforward comparison of the speed with which they are able to induce emesis.

ICI is committed to reductions in the hazard of paraquat formulations and the inclusion of the emetic is an important part of this worldwide. It is usually not practically possible to obtain definitive epidemiological data on the effectiveness of the emetic since accurate information on the quantity ingested and the time between ingestion and treatment is seldom available. ICI's own experience and anecdotal evidence indicates that the emetic improves the survival of patients who have swallowed small doses through its combined effects of dose reduction and rapid hospitalisation. The survival rate in patients who have accidentally ingested paraquat has been very good. However in patients who have ingested large doses survival continues to be poor since the dose ingested is so great that in spite of the emesis induced sufficient paraquat is still present to cause a fatality.'

Author: Stephanie A Schulz

Date: 07-Jan-1993 16:28

TO: Tim Pastoor

(PASTOOR TP@Al@UWGVAX)

Subject : pq info revised

Tim, after discussions with Janice Reed, I have updated the PQ formulation info you asked for. I originally used the "Label Declaration of active ingredient" because Wayne felt we always used that number when discussing product formulation, given that is what the EPA looks at. However, for our purposes -- Production, we are interested in what amount we start with of all Paraquat concentrate, then the dichloride/ion/impurities action can take place.

So.. I have modified the chart to include a paraquat concentrate column and a Paraquat Ion (label% listed and then the other ingredients. I also changed the other ingredient(water) column to read "Water and other impurities", because Janice said we should refer to that which we can't get rid of (manufacturing/chemically impossible) as impurities.

For number crunching, these new numbers will probably make more "sense" to the crunchers because they list what is started with to make a 1000lb of product. The crunchers are probably on concerned with how much paraquat concentrate 3 we start with and not what is actual AI due to chemistry.

My numbers are still listed in % of formulation.

| Product | PQ Con. | PQ+ Ion | Emetic | Valeric acid | Color | Water/other impurities |
|----------|------------|------------|--------|-----------------|-------|---------------------------|
| PQcon3* | 98.97 | (43.5) | 0.101 | 0.841 | 0.084 | 0.004 |
| Extra | 82.55 | (37.05) | 0.053 | 0.440 | 0.044 | 16.913 |
| Super | 51.761 | (23.39) | 0.053 | 0.440 | 0.044 | 47.702 |
| Cyclone* | 64.81 | (29.10) | 0.055 | 0.500 | ----- | 34.635 |
| Starfire | 51.761 | (23.39) | 0.053 | 0.440 | 0.044 | 47.702 |

Note:

+ Label declaration of active ingredient

* Alternate Formulation that includes emetic.

Author: PASTOOR TP@A1@UWGVAX

Date: 07-Jan-1993 18:56

TO: Bob Scott [CTL]

(SCOTT RC @ A1 @ APVXC1)

Subject : PQ

I'm sending you a message from Stephanie Schulz, who is in my group and who seems to find new and slightly different information on PQ products every day. Since she is such a thorough person, she asked a few more questions and came up with the following data. I hope this information is helpful...

Author: PASTOOR TP@A1@UWGVAX

Date: 06-Jan-1993 19:04

TO: Bob Scott [CTL]
CC: Stephen L Heying
CC: Wayne Hillebrecht

(SCOTT RC @ A1 @ APVXC1)
(HEYING SL@A1@UWGVAX)
(HILLEBRECHT WR@A1@UWGVAX)

Subject : PQ Concentrations

Bob,

Here is the information you requested so that you can provide Saba with guidance in his views towards reducing the concentration of emetic in PQ products.

Percent in Formulation

| Product | [PQ] | [emetic] | [Valeric acid] | [color] | Other Ingred (water,etc.) |
|----------|-------|----------|-------------------|---------|------------------------------|
| Teen | 43.5 | | | | 56.5 |
| Extra | 37.05 | 0.053 | 0.440 | 0.044 | 62.413 |
| Super | 23.39 | 0.053 | 0.440 | 0.044 | 76.073 |
| Cyclone | 29.10 | 0.055 | 0.500 | ----- | 70.345 |
| Starfire | 23.39 | 0.053 | 0.440 | 0.044 | 62.413 |

[Info based on Confidential Statements of Formulation for each product and on Wayne Hillebrecht. PQ % based on "Label Declaration of Active Paraquat Dichloride."]

Author: Bob Scott [CTL]

Date: 12-Jan-1993 10:40

TO: Remote Addressee

(tp@a1@uwgvax)

CC: N.N. Sabapathy

(SABAPATHY NN@a1@FHVAXC)

CC: Stan Chart

(CHART IS@a1@FHVAXC)

Subject : PP796 Inclusion Levels

Tim,

I am able to provide some comments on the letter from Steve Heyings.

Based on an assessment of the available animal and human data on the emetic effects of PP796 it was decided that a dose of 5mg was needed to ensure early and effective emesis. Thus, for a 70kg individual this represents a dose of 0.07mg/kg. This dose is precisely in the effective range as cited in Steve Heyings letter (0.03-0.11).

This dose must be present in the minimum potentially toxic dose of a PQ formulation. Although no absolute data are available for MAN, the MLD is considered to be around 40mg/kg, or, around 3000mg in a 70kg man.. This amount would be present in about 15ml of a 200g/l PQ ion formulation). Thus, the minimally potentially toxic dose is less than 40mg/kg and so the effective dose of PP796 must be present in a volume of formulation which is less than the MLD volume.

It was decided that the effective dose must be present in a 10ml volume of a 200g/l formulation.

Thus, 5mg must be contained in 10ml i.e 0.5mg/ml, or 0.05%.

All the information you sent me indicated that PP796 is present at this level in your products. It seems that you have it right, based on the original decisions for inclusion levels.

I can understand how Steve arrived at his suggestion that the PP796 levels are, perhaps, too high by a factor of 10. He has assumed that an (reliable) effective dose can be as low as 0.03mg/kg and that this can be present in a volume of formulation which is regarded as 2X MLD volume. This is not the position we can support.

I hope this clarifies the situation and you can assure Steve that the PP796 inclusion levels are indeed NOT 10X too high in your products.

Bob.

Author: PASTOOR TP@A1@UWGVAX

Date: 06-Jan-1993 20:54

TO: Bob Scott [CTL]

(SCOTT RC @ A1 @ APVXC1)

CC: Stephen L Heying

(HEYING SL@A1@UWGVAX)

CC: Stephanie A Schulz

(SCHULZ SA@A1@UWGVAX)

CC: Wayne Hillebrecht

(HILLEBRECHT WR@A1@UWGVAX)

Subject : PQ Concentrations/followup

Bob,

Please add the following to the table I sent you:

| | PQ | emetiC | VA | color | Other |
|------|-------|--------|-------|-------|--------|
| | ----- | ----- | ----- | ----- | ----- |
| Tech | 44.91 | 0.101 | 0.842 | 0.019 | 54.128 |

From:
Bob Scott [CTL], CTL
Alderley Park (Ext [Redacted - EU PII])

Date:
05-Jan-1993

Document Ref:

To:
Dr.NN Sabapathy

Copies to:
IS Chart
D Castles
A Cook

PQ EMETIC LEVELS

Saba,

Having now returned from holiday I have found in my mail an interesting enquiry from Tim Pastoor about emetic levels in PQ formulations. This letter was also sent to you and Becky Sherman. I do not propose at this time to respond to Tim. I suggest that you do this and I will write to Tim to tell him you are dealing with this issue. Will you please copy me with anything you send to Tim so I know what is being said.

This seems a good way to welcome the New Year.

Best wishes,

Bob.

Author: Bob Scott [CTL]

Date: 05-Jan-1993 11:32

TO: N.N. Sabapathy
CC: Diane Castle
CC: Stan Chart
CC: Steve Cook

(SABAPATHY NN@A1@FHVAXC)
(CASTLE DL@A1@FHVAXC)
(CHART IS@A1@FHVAXC)
(COOK SE @ A1 @ UWPOO)

Subject : Pq Emetic concentration

200g/L
2g/mL
2g/10mL

Exotic levels in PQ populations

Current minimum inclusion level of P1796 = 0.05%

This level is derived upon ~~an~~ ^{the} available evidence indicates

that 5mg is an effective human dose to induce immunity

and, thus, this amount should be present in a minimum

level oral dose (approx. 10mL).

P1796: 5mg in a 70kg adult = 0.07mg/kg
(reported effective range: 0.03 - 0.11g/kg)

PQ Concentration, 200g/L : 10mL = 2.0g PQ
∴ for 70kg adult = 29mg/kg = oral MLD.

DOCUMENT A: PRODUCT CHEMISTRY

January 23, 1991, EPA requested that ICI submit essentially an entire product history battery on the two "formulators intermediates (FI)" as they understood them to be 43.5% PQ dichloride and 29.1% PQ dichloride. ICI previously provided data for the chemical solid produced under laboratory conditions. This data was included in MRID 9001 and in an addendum (MRID 40624701). This confused the agency into thinking paraquat TGAI is a solid when it is actually a liquid of 53.8% PQ dichloride as now produced at the Bayport facility. This liquid 53.8% TGAI is unregistered which is unacceptable to EPA.

A also needed to know how we go from 53.8% PQ dichloride to the manufacturer's use product EPA Reg. No. 10182-115 (43.5% PQ dichloride + water) and its alternate formulations, (which we have now presented as dilutions of the 53.8% by adding water, emitic, stench, and valeric acid. We have submitted revised CSF's to EPA as follows:

| <u>Manufacturer's Use Product Name</u> | <u>End Use Product Made from MUP</u> | <u>EPA Reg. No.</u> | <u>CSF No.</u> | <u>Ingredients</u> |
|--|--------------------------------------|---------------------|----------------|--|
| paraquat Concentrate 3 | none | 10182-115 | 0107 | paraquat ion; impurities; and water |
| paraquat Concentrate 3 | Gramoxone Super | 10182-115 | 0108 | paraquat ion; impurities; water; valeric acid @0.84%; FD & C Blue No. 1 @ 0.084%; and PP796 @ 0.10% |
| paraquat Concentrate 3 | Gramoxone Extra | 10182-115 | 0113 | paraquat ion; impurities; water; valeric acid @ 0.84%; FD & C Blue No. 1 @ 0.084%; and PP796 @ 0.06% 2/12/91/gm. |
| paraquat Concentrate 3 | Cyclone | 10182-115 | 0114 | paraquat ion; impurities; water; valeric acid @ 0.84%; and PP796 @ 0.08% 2/12/91/gm. |

These formulations with the 3 additives of PP796 (emitic); Valeric Acid (stench); and/or dye were submitted as alternate formulations to 10182-115. This is the strategy that had

Startfire for para

From:
Bob Scott [CTL], CTL
Alderley Park (Ext Redacted - EU PII)

Date:
05-Jan-1993

Document Ref:

To:
Tim Pastoor

Copies to:
Dr.NN Sabapathy

PQ EMETIC CONCENTRATION

Tim,

Nice to hear from you and I hope ypu are well. Thanks for the letter about PP796 levels. I think this is one for Saba to deal with although I will assist if necessary. I have asked Saba to reply to you and copy me with anything he sends across to you.

Best wishes,
Bob.

Author: PASTOOR TP@A1@UWGVAX

TO: Bob Scott [CTL]
TO: N.N. Sabapathy
TO: Becky Sherman
CC: Stephen L Heying

(SC
(SA
(SH
(HEY

Send AIO to Tim
14/12 asking if
request could
wait for Bob's
return.

Jian
Angela
Don Carillo

Subject : PQ Emetic and Stench Concentrations

To: Becky Sherman
Bob Scott (CTL)
Dr. Sabapathy (Fernhurst)

From: Tim Pastoor

Subj: PQ Emetic and Stench Concentrations.

Steve Heying was asking for "scientific" rationale that establish the effective concentrations of stench and emetic in paraquat products. His reason is that we can reduce formulation costs if we reduce concentrations of these additives. In addition, we've received complaints that the stench "stinks too much."

Becky, I know you and I visited this question sometime in the last year. We assembled information on the emetic concentration and you may also have looked at the stench concentration. You wrote the attached memo, and as a result some decisions were taken that I cannot recall nor do I have on record. Do you have a file on this issue? If so, where?

Bob, are you familiar with this issue? Could you please contribute your views?

Saba, I believe you were in on these discussions in the last year or so. Could you please give a brief recap of your disposition on this issue?

Thank you.

- Tim

++++
(attachment)

Delivery: Tim Pastoor
Date: 18-Jan-1992 13:57 EST
From: Becky Sherman
SHERMAN B.E.
Dept: R&RA
Tel No: Redacted - EU PII

TO: Remote Addressee
FHLVAX)

(CRISP G.N. AT A1 AT

CC: Russ Rising

(PAPER MAIL)

Author: PASTOOR TP@A1@UWGVAX

Date: 11-Dec-1992 16:39

TO: Bob Scott [CTL] (SCOTT RC @ A1 @ APVXCI)
TO: N.N. Sabapathy (SABAPATHY NN@A1@FHVAXC)
TO: Becky Sherman (SHERMAN BE@A1@UWGVAX)
CC: Stephen L Heying (HEYING SL@A1@UWGVAX)

Subject : PQ Emetic and Stench Concentrations

To: Becky Sherman
Bob Scott (CTL)
Dr. Sabapathy (Fernhurst)

From: Tim Pastoor

Subj: PQ Emetic and Stench Concentrations.

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+++++
(attachment)

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Date: 18-Jan-1992 13:57 EST
From: Becky Sherman
SHERMAN B.E.
Dept: R&RA
Tel No: Redacted - EU PII

TO: Remote Addressee
FH1VAX)

(CRISP G.N. AT A1 AT

CC: Russ Rising

(PAPER MAIL)

From: Bob Scott - CTL
SCOTT RC

Date: 20-Feb-1995 15:13

Subject: Bipyridyl RIM ; Draft Agenda

John Ishmael and I met this am to discuss the possible Agenda for the RIM (16th March). After this Robin Birtley called to discuss additional Fernhurst ideas (marked *).

Below is a proposed Agenda (with some notes). Please send me your views. This will form the basis of our pre-RIM meeting on 27th February, HG1, 14.00-17.00h.

PROPOSED AGENDA

1. Neuroinvolvement

- a) Evidence of neurological effects in Man RCS
(based on Draft overview in preparation)
- b) Absorption through the blood brain barrier and effects on developmental behaviour EAL
(to include data from MRC)
- c) PQ vs MPTP ; review of progress and future plans EAL

2. Antidotes/treatments

- Parenteral MgSO4 studies in the rat JRH
- Clinical application MFW

3. EU Review

- Paraquat lung uptake ; most relevant animal model for man EAL
(Review of NOEL/NOAEL for sub- and chronic studies;
CTL position on species' Km and Vmax values; ✓
relevance of the dog vs rat;
* are there any other studies we could do to understand
plasma levels vs lung toxicity etc)

~~NOEL in rat 2-year study~~

4. Rabbit developmental toxicity

- *Alternative species to the rabbit for a new paraquat study ✓ RCS

5. Rabbit developmental toxicity study status with CalEPA RCS

AOB: US para

Bob

Distribution:

| | |
|-------------------|------------------|
| TO: John Ishmael | (ISHMAEL J1) |
| TO: Iain Purchase | (PURCHASE IFH) |
| TO: Jon Heylings | (HEYLINGS JR) |
| TO: Edward Lock | (LOCK EA) |
| TO: James Mackay | (MACKAY JM) |

CC: Leetch M.S.
CC: Bob Ridsdale
CC: Wayne Hillebrecht

(LEETCH M.S.)
(RIDSDALE R.E.)
(HILLEBRECHT W.R.)

Boyle, 1973

Subject: EMITIC LEVELS IN PARAQUAT FORMULATIONS

It has come to our attention that emetic levels in paraquat formulations in the US are about 10X the level indicated in the PP796 MSDS as acceptable to cause emesis in humans (the range to cause emesis is 0.03 - 0.11 mg/kg). When calculations are done assuming a 30 ml mouthful and a 70 kg man, then we are putting 10X more emetic than the 0.03 mg/kg level. Apparently the costs of emetic has gone up about 4X over the last two years and the 10X amount we are now putting in the formulation costs ICI Americas about \$800,000 more than putting the 1X level.

We would like to reduce the level of emetic in the formulation if this can be done safely and still have the emesis effect. Could you investigate this or let me know what information I need to put together to demonstrate our request to make a reduction.

While we are on this subject, everything I read these days about a new and improved paraquat formulation talks in terms of increasing the capacity of the PP796 plant by 4X. I do not understand why this is necessary. Are we plannin' to put more emetic in the formulation? If so, I do not understand why. It would seem that the same amount of emetic on a volume basis would always be required in the formulation to cause emesis. Can you shed some light on this also?

Thanks,

| | | | |
|--------------------------|-------------------------|---------|---------|
| <u>USA formulations:</u> | Gramoxone Super | - PP796 | 0.10% |
| | PP Gramoxone | PP796 | 0.06% |
| | Gramoxone Extra | PP796 | @ 0.08% |
| | Cyclone | | |

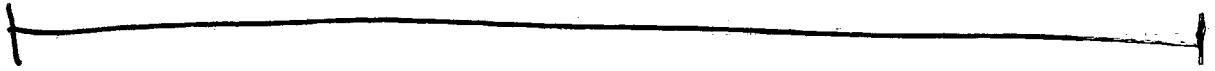
PQ Emeter

PP796.

level included in formulation at $0.05\% w/v$ to ensure dose of 5mg in 10ml of 200g/l_l formulation.
10ml believed to be the minimum potential lethal volume.

① $0.05\% \equiv 0.5mg/ml$

$\therefore 10ml \equiv 5mg \equiv$ effective dose to induce vomiting.



Steve Heyings letter: rebuttal.

① 30ml mouthful = 15mgs
for 70Kg man = $\frac{15}{70} = 0.2$

10ml = 5mgs
for 70Kg man = $\frac{5}{70} = \underline{\underline{0.07mg/Kg}}$

$1g = 1ml$
 $1000mg = 1ml$
 $\frac{50}{1000} = 0.05$

$50mg/100ml$
 $\frac{50}{100} = 0.5$
 $\frac{0.5}{10} = 0.05$

200g/l_l
200mg/ml
30ml = 15

0.5mg/ml.

5mg in 10ml.
0.5mg in 1ml.

5mg = 10ml
 $\frac{50mg}{100ml}$
 $\frac{50mg}{1000ml}$
0.05

30ml =
 $\frac{30 \times 200}{60}$

$$MLD = 40 \text{ mg/Kg.}$$

$$\therefore \times 70 = 3000 \text{ mg.}$$

$$\begin{aligned} \text{Grunerone} &= 200 \text{ g/l} \\ &\text{or } 200 \text{ mg/ml.} \\ \therefore &\quad \quad \quad \underline{15 \text{ ml.}} \end{aligned}$$

$$40 \text{ mg/Kg} \times 70$$

$$0.03 \text{ mg/Kg in}$$

$$\text{Dose} = 0.03$$

$$\text{Dose} = 30 \text{ ml}$$

$$\text{Need} = 0.03 \text{ mg/Kg}$$

$$\therefore \text{ need } 0.03 \times 70 =$$

$$\underline{\underline{2.1 \text{ mg}}}$$

$$\text{in } 30 \text{ ml}$$

$$= 0.07 \text{ mg/ml}$$

$$=$$

$$0.05\% = 0.5 \text{ mg/ml}$$

$$\therefore 30 \text{ ml} = 150 \text{ mg.} \quad \frac{15}{70} = 0.2$$

PP796 [2-amino-6-methyl-5-oxo-4-n-propyl-4,5-dihydro-s-triazolo (1,5-a) pyrimidine) is a centrally-acting phospho-diesterase emetic agent which is added to paraquat formulations. This paper explains the lack of human side-effects from exposure to PP796 and confirms the benefit of addition to paraquat formulations.

PP796 : Lack of evidence of potential side-effects from human exposure

Toxicology data

Human exposure to PP796 will occur as a consequence of ingestion of GRAMOXONE or other paraquat-containing products. To assess the toxicological significance of this route of exposure a wide range of studies have been completed with PP796 using oral dosing or dietary administration.

The acute oral MLD values of PP796 in rats and mice have been found to be 100 and 300mg/kg/d, respectively.

PP796 has been administered to rats and dogs in food for 3 months. In the rat study the top dose administered was 5mg/kg/day and in the dog study 1.5mg/kg/day. PP796 had no effect on the haematology, organ weights or histopathology in the rats as a consequence of this dosing regime. Similarly, in dogs, there were no effects on haematological and biochemical parameters, no histopathology findings and in addition, no effect on blood pressure, heart or respiration rate and measured ECG-activity. After dosing some test animals in these top dose group were placed on normal diet ie containing no PP796, for a period up to 12 weeks. There were no changes in these animals attributable to PP796.

Oral dosing was also used to study the teratological potential of PP796 in rats and rabbits. The rats and rabbits were given daily doses of up to 1.25mg/kg/day. In these studies, which involved daily dosing of PP796 to pregnant animals, PP796 had no teratogenic effect and no significant effect on pregnancy, littering and weaning.

Relevance to deliberate human exposure

It is reported that a fatal oral dose of GRAMOXONE to a man is approximately 15ml. PP796 is present in GRAMOXONE at a concentration of 0.05%, which is equivalent to 0.5mg/ml. The amount of PP796 in a potentially fatal dose, therefore, is 7.5mg.

If this amount is deliberately ingested by a man of 60kg body weight, then the dose of PP796 will be 0.125mg/kg.

This dose can be compared with the doses which have been shown to cause no toxicity in multiple oral dosing studies (see above). The lowest top dose in any of the studies described above, which was shown to cause no significant toxicity, was the 1.25mg/kg/day given to pregnant animals in the teratology studies.

This dose is 10 times higher than the dose of PP796 contained in a fatal dose of GRAMOXONE.

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A further comparison can be made between the amount of PP796 in a fatal dose of GRAMOXONE and the lowest reported acute oral MLD value of 100mg/kg (in the rat). This shows that such a fatal dose contains only an 800th of the oral MLD amount of PP796.

These data indicate that no toxicological consequences can be expected from human exposure to PP796 in GRAMOXONE or other paraquat-containing formulations.

PP796 : Affect on mortality

In the 1970s Zeneca recognised that GRAMOXONE, especially after decanting from an original container, could be mistaken for some common beverages. At this time, also, Gramoxone fatalities from deliberate and accidental ingestions began to increase. Zeneca reacted swiftly to alter GRAMOXONE and make it safer. Three measures were taken 1) addition of a colouring agent 2) addition of a pungent alerting agent and of course, 3) addition of PP796, the emetic agent. These 3 measures meant that within a short time period the product changed significantly.

These changes removed from the market place the source of non-emeticised GRAMOXONE. This has made it extremely difficult to obtain scientifically valid data to prove the added safety conferred by the presence of the emetic ie. data acquisition, in the same time period, on non-emeticised formulation compared with emeticised.

The emetic was added to the formulation to induce assured, early, effective vomiting. Such vomiting is necessary to rapidly remove paraquat from the stomach after ingestion and so reduce systemic absorption. The amount of contemporaneous data which are available for such a comparison are naturally limited.

One way to assess the benefit of the emetic requires scientific data to prove that the emetic induced earlier effective emesis, in man, compared with non-emeticised material. Such an assessment was undertaken by Zeneca (then ICI) using data collected by the UK National Poisons Information Service on over 500 cases reported over a relevant time between 1979-1984. The emetic was believed to have been present in at least 120 of the poisoning cases.

These data clearly showed that the addition of the emetic to paraquat formulations markedly improved the reliability of induction of vomiting and that in most cases the emetic led to an earlier onset of vomiting compared with the non-emeticised material. This is precisely what had been hoped for and scientifically, predicted to be the benefit of adding PP796 to the formulations.

Whilst these data cannot be used to pronounce definitively on whether the emetic reduced fatalities- interpretation is complicated, for example, as the different physicians used a variety of treatment regimes which might have affected the prognosis- the data did indicate that mortality did decrease.

Conclusion

It is our contention that the presence of the emetic in paraquat formulations is an essential and useful safening agent.

RC Scott, Product Toxicologist (27/5/94)

TO WHOM IT MAY CONCERN

PP796 [2-amino-6-methyl-5-oxo-4-n-propyl-4,5-dihydro-s-triazolo (1,5-a) pyrimidine) is a centrally-acting phospho-diesterase emetic agent which is added to paraquat formulations. This paper explains the lack of human side-effects from exposure to PP796 and confirms the benefit of addition to paraquat formulations.

PP796 : Lack of evidence of potential side-effects from human exposure

Toxicology data

Human exposure to PP796 will occur as a consequence of ingestion of GRAMOXONE or other paraquat-containing products. To assess the toxicological significance of this route of exposure a wide range of studies have been completed with PP796 using oral dosing or dietary administration.

The acute oral MLD values of PP796 in rats and mice have been found to be 100 and 300mg/kg/d, respectively.

PP796 has been administered to rats and dogs in food for 3 months. In the rat study the top dose administered was 5mg/kg/day and in the dog study 1.5mg/kg/day. PP796 had no affect on the haematology, organ weights or histopathology in the rats as a consequence of this dosing regime. Similarly, in dogs, there were no affects on haematological and biochemical parameters, no histopathology findings and in addition, no affect on blood pressure, heart or respiration rate and measured ECG-activity. After dosing some test animals in these top dose group were placed on normal diet ie containing no PP796, for a period up to 12 weeks. There were no changes in these animals attributable to PP796.

Oral dosing was also used to study the teratological potential of PP796 in rats and rabbits. The rats and rabbits were given daily doses of up to 1.25mg/kg/day. In these studies, which involved daily dosing of PP796 to pregnant animals, PP796 had no teratogenic affect and no significant affect on pregnancy, littering and weaning.

Relevance to deliberate human exposure

It is reported that a fatal oral dose of GRAMOXONE to a man is approximately 15ml. PP796 is present in GRAMOXONE at a concentration of 0.05%, which is equivalent to 0.5mg/ml. The amount of PP796 in a potentially fatal dose, therefore, is 7.5mg.

If this amount is deliberately ingested by a man of 60kg body weight, then the dose of PP796 will be 0.125mg/kg.

This dose can be compared with the doses which have been shown to cause no toxicity in multiple oral dosing studies (see above). The lowest top dose in any of the studies described above, which was shown to cause no significant toxicity, was the 1.25mg/kg/day given to pregnant animals in the teratology studies.

This dose is 10 times higher than the dose of PP796 contained in a fatal dose of GRAMOXONE.

A further comparison can be made between the amount of PP796 in a fatal dose of GRAMOXONE and the lowest reported acute oral MLD value of 100mg/kg (in the rat). This shows that such a fatal dose contains only an 800th of the oral MLD amount of PP796.

These data indicate that no toxicological consequences can be expected from human exposure to PP796 in GRAMOXONE or other paraquat-containing formulations.

PP796 : Affect on mortality

In the 1970s Zeneca recognised that GRAMOXONE, especially after decanting from an original container, could be mistaken for some common beverages. At this time, also, Gramoxone fatalities from deliberate and accidental ingestions began to increase. Zeneca reacted swiftly to alter GRAMOXONE and make it safer. Three measures were taken 1) addition of a colouring agent 2) addition of a pungent alerting agent and of course, 3) addition of PP796, the emetic agent.

These 3 measures meant that within a short time period the product changed significantly.

These changes removed from the market place the source of non-emeticised GRAMOXONE. This has made it extremely difficult to obtain scientifically valid data to prove the added safety conferred by the presence of the emetic ie. data acquisition, in the same time period, on non-emeticised formulation compared with emeticised.

The emetic was added to the formulation to induce assured, early, effective vomiting. Such vomiting is necessary to rapidly remove paraquat from the stomach after ingestion and so reduce systemic absorption. The amount of contemporaneous data which are available for such a comparison are naturally limited.

One way to assess the benefit of the emetic requires scientific data to prove that the emetic induced earlier effective emesis, in man, compared with non-emeticised material. Such an assessment was undertaken by Zeneca (then ICI) using data collected by the UK National Poisons Information Service on over 500 cases reported over a relevant time between 1979-1984. The emetic was believed to have been present in at least 120 of the poisoning cases.

These data clearly showed that the addition of the emetic to paraquat formulations markedly improved the reliability of induction of vomiting and that in most cases the emetic led to an earlier onset of vomiting compared with the non-emeticised material. This is precisely what had been hoped for and scientifically, predicted to be the benefit of adding PP796 to the formulations.

Whilst these data cannot be used to pronounce definitively on whether the emetic reduced fatalities- interpretation is complicated, for example, as the different physicians used a variety of treatment regimes which might have affected the prognosis- the data did indicate that mortality did decrease.

Conclusion

It is our contention that the presence of the emetic in paraquat formulations is an essential and useful safening agent.

From: Sally Cook
COOK S@A1@FHVAXC

Date: 29-Apr-1994 09:30

TO: Bob Scott [CTL]
CC: Jane Hall
CC: Andy Cook

(SCOTT RC @ A1 @ APVXC1)
(HALL J@A1@FHVAXC)
(COOK AR@A1@FHVAXC)

Subject: SIDE-EFFECTS OF THE EMETIC IN PARAQUAT FORMULATIONS - MY

Dear Bob

I have spoken to Saba and following your earlier rebuttal document for Malaysia regarding the side-effects of the emetic, I would be grateful for your help again.

To assist in further clarifying views on the emetic I need information to help with the following requests from Malaysia:

1. Scientific data to show that the emetic will not/does not produce side-effects.
2. Scientific data to show that the addition of emetic worldwide is beneficial in reducing mortality rates during suicidal or accidental poisoning.

Please could I have your comments during May.

Thank You and Regards
Sally

① — a) Toxicology
b) Coc letter.

② papers marked.

From: Sally Cook
COOK S@A1@FHVAXC

Date: 29-Apr-1994 09:30

TO: Bob Scott [CTL] (SCOTT RC @ A1 @ APVXC1)
CC: Jane Hall (HALL J@A1@FHVAXC)
CC: Andy Cook (COOK AR@A1@FHVAXC)

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Thank You and Regards
Sally

From: Bob Scott - CTL
SCOTT RC

Date: 23-Mar-1994 13:34

TO: Sally Cook

(COOK S@A1@FHVAXC)

Subject: Side-effects of the emetic in PQ formulations.

SIDE-EFFECTS OF THE EMETIC IN PARAQUAT FORMULATIONS

Zeneca is pleased to have the opportunity to comment on the published scientific papers by Noguchi et al and by Yamashita et al on the emetic in paraquat formulations.

Noguchi et al claim that the emetic in Gramoxone can cause cardio-respiratory effects in Wistar rats. Whilst the data reported are interesting the experimental design is flawed.

In this study the paraquat was administered, whether formulated product (Gramoxone, which contains emetic, or Paragreen A, which does not) or aqueous paraquat, by intravenous injection. Zeneca considers that this route of administration is not relevant to assessing the effects of human exposure to paraquat products.

The effects reported were a consequence of dosing approximately 10 times the paraquat median lethal dose (MLD). Under these conditions the toxicity of paraquat itself would be of primary importance and the contribution of any other formulation component, including the emetic, would be insignificant. In order to establish any effect of the emetic normal accepted scientific practice would dictate that the effect of the emetic alone should have been studied; this has not been done.

Without such fundamental control data and the choice of a protocol which is irrelevant to understanding the consequences of human exposure to paraquat formulations this publication cannot be regarded as a source of reliable data on the possible cardio-respiratory effects of the emetic in man.

Yamashita et al have studied the effect of the emetic in sedated dogs. They dosed the dogs by intubation into the stomach with paraquat in either a formulation or an aqueous preparation. Dose levels of 30 and 250mg/kg were used. These dose levels are very high (approximately 2 and 20 times the MLD for paraquat in dogs).

They reported that the presence of the emetic caused early emesis in the dogs in contrast to no emesis when the emetic was absent.

There was a difference in paraquat absorption as indicated by plasma paraquat levels measured over the first 4 hours after dosing from the lower dose but no difference, however, at the higher dose. Their opinion was that at the higher dose level the emetic made no difference to bioavailability.

Unfortunately the protocol used to obtain these comparison data is scientifically flawed. These workers have used a commercially available formulation and compared the effect with those of an aqueous preparation; thus, the presence or absence of the emetic was not the only variable. In addition the dogs were sedated and the effect of sedation on absorption has not been determined. More significant, however, was that bioavailability was only assessed over a 4 hour period. It is our experience, in the dog, that in order to compare the bioavailability of paraquat from different doses or formulations that a longer time period is necessary and data obtained over only 4 hours is very misleading. For these reasons Zeneca believes that the information in this paper is of very limited value for the assessment of the effect of the emetic.

Zeneca believes that the presence of the emetic in paraquat formulations is a valuable component to enhance the safety of formulations. These two publications do not provide data which would cause us to change this opinion.

Dr.RC Scott

Product Toxicologist (25/03/94)

From: Jon Heylings
HEYLINGS JR

Date: 23-Mar-1994 09:28

TO: Bob Scott - CTL

(SCOTT RC)

Subject: Paraquat Emetic

Bob,

Following our conversation yesterday on potential theophylline-like effects of PP796 I have checked my files for extra information.

Firstly, the human volunteer studies at Pharms used up to double the dose of PP796 that a lethal PQ dose would provide and its acute and chronic tox (from animal studies) is quoted as low. Thus, in man, one would presume that you would have to take in a very large volume of product to cause PP796 side-effects apart from vomiting.

CTL dog studies (Robinson ad Brammer) only showed side effects at 20mg/kg PP796 which is equivalent to 4 lethal PQ doses in man for the level in Gramoxone. Our dog studies where we have given Magnoxone at 20X the lethal PQ dose containing 3X the current level of emetic only produced rapid vomiting as the side-effect.

I do not agree with the conclusions of Yamashita et al since plasma PQ up to 4 hours does not provide enough information to say that AUC will be high or low. The other problem is that the expt is incorrectly controlled with non emeticised PQ also being devoid of all the many other formulation adjuvants.

Finally, on a somewhat separate note, the indication that some territories may be suggesting actually removing the emetic astounds me. The evidence for its benefit has always been controversial but in the absence of a thorough appraisal of its "effective concentration in man" (which as you know was never reviewed and reported in 1991) important evidence continues to be disregarded.

Jon

7163
From: Sally Cook
COOK S@A1@FHVAXC

Date: 21-Mar-1994 13:20

TO: Bob Scott [CTL]
CC: Roger J Parker
CC: Andy Cook

(SCOTT RC @ A1 @ APVXC1)
(PARKER RJ@A1@FHVAXC)
(COOK AR@A1@FHVAXC)

Subject: SIDE-EFFECTS OF ADDING EMETIC - PARAQUAT/MALAYSIA

Dear Bob

We have been having correspondence with ICI (Agrochemicals) Malaysia regarding proposed Malaysian specifications for paraquat aqueous solutions. Further to a recent meeting reviewing the proposed draft and ZENECA's comments, we have had further queries from the Pesticides Board in Malaysia and I would appreciate your help with the following.

The Pesticide Board have said that they have received reports from studies in Japan indicating side-effects of adding emetic and have invited our comments and clarification. The two reports, detailed below, (copies attached with faxed copy of message), have been received from the Pesticide Board who already have preconceived ideas on the redundancy and side-effects of emetic. I would be grateful if you could help redress this situation by preparing a rebuttal.

I am afraid, as usual, we do not have much time to do this and I need your response by Thursday 24th March, latest, to enable my colleague in Malaysia to be fully prepared when he attends the next meeting.

Thank you for your help.

Best Wishes
Sally Cook

Friday 25th March

13/14 April

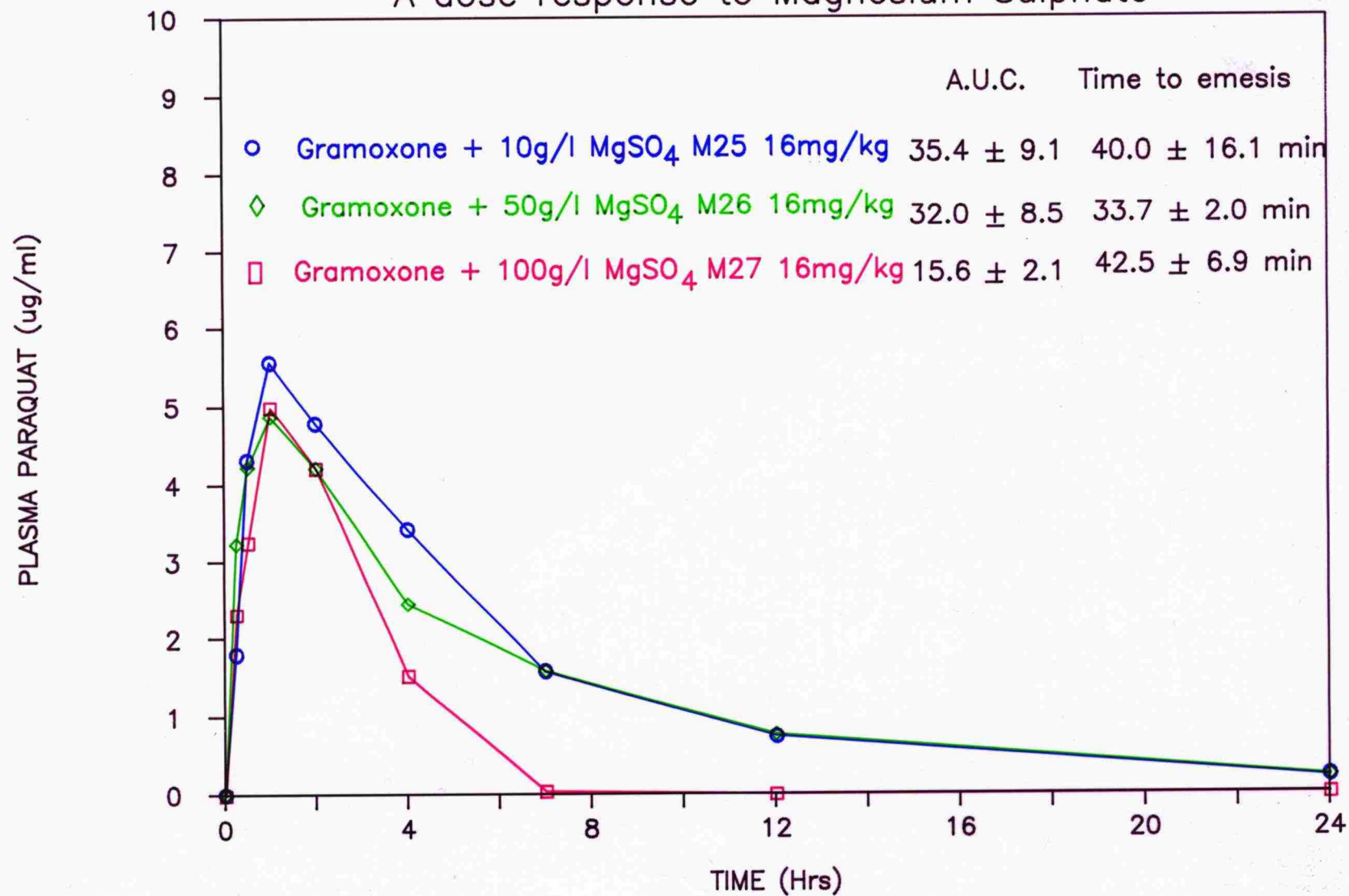
ATTACHED WITH FAXED COPY OF MESSAGE

Noguchi, N. et. al. "Cardio-respiratory Effects on Paraquat with and without Emetics on Wister Rats" Vet Hum Toxicol 27 (6) December 1985

Yamashita, M. et. al. "The Plasma Paraquat Concentration of Dogs administered Paraquat with Emetic" Vet Hum Toxicol, Supplement 1982

FORMULATION STUDIES XD1328

A dose response to Magnesium Sulphate





ICI Japan Limited

Central PO Box No 411
Tokyo 100-91 Japan

From : A Calderbank

To : Dr R Birtley

Telephone 211-6661/9
Telex 0222-2381 (2222381 ICITOK J)
Telegram impkemix Tokyo

cc : Dr J Sanderson
Dr L L Smith ✓
Dr T B Hart

Your ref

Our ref

Date

AC/js

18 Mar 1986

Dear Robin

You asked what I would suggest in the way of experimentation to clear the way for increasing the level of emetic in PQ formulations.

I would suggest we need to do some studies in a non-vomiting species, such as the rat and rabbit (same animals used by Misawa), paraquat with and without emetic and emetic alone. Evaluate clinically for heart effects (ECG) possibly blood enzymes and look for cardiovascular and heart muscle defects histopathologically at post mortem.

This is purely off the top of my head and hopefully I can discuss this in more detail with Lewis when he arrives here in April.

Incidentally I came across another surprising result in the Pharms report Vol III Toxicology of the emetic.

The emetic seems to be about twice as toxic as paraquat to rabbits by iv injection (LD50 PQ 18mg/kg, PP796 5 - 10mg/kg).

Since the emetic is absorbed more readily than PQ it suggests the oral LD50 values might differ even more widely. What is perhaps worrying is that it also suggests a very large difference in susceptibility of different animals to the emetic. Perhaps we should check the Pharms iv figure and determine an oral LD50 value for rabbits.

Please find enclosed my third attempt at rebutting Misawa's claim that the emetic contributes to fatalities in Gramoxone poisoning.

Since this will be going in to MAFF I have had to include only those statements which could be backed by proper evidence. It also helps if the evidence is from a Japanese source.

Any comments would be welcome and thanks to those who provided information and ideas.

Also enclosed a copy of my notes of a discussion with Professor Yamashita, Institute of Clinical Medicine, Tsukuba University.

Best regards.

Yours sincerely

Alan

A Calderbank

A subsidiary company of Imperial Chemical Industries PLC

SYNG-PQ-04262370_R

VALUE OF EMETIC (PP796) USED IN GRAMOXONE

Background

Misawa et al have claimed that 'Gramoxone' (PQ + emetic) is more toxic than 'Paragreen' (a formulation of PQ without emetic) and paraquat alone, by virtue of the action of the emetic on the heart.

The authors have subsequently modified their claim recognising two forms of toxicity leading to death, viz

- (i) Small amounts of 'Gramoxone' leading to pulmonary fibrosis and delayed death due to respiratory failure.
They recognise that this is typical PQ poisoning.
- (ii) Large amounts of 'Gramoxone' with death following quickly. The authors claim that the emetic is causing damage to the heart leading to cardiac arrest before the lungs are affected by PQ.

Misawa Experiments

One can criticise the Misawa experiments which involved injection of the products directly into the blood of rats and rabbits at almost ten times the dose shown to kill these animals with paraquat alone. No experiment was conducted with emetic alone.

The experiments were unscientific and unrealistic of the practical situation (oral ingestion).

However, the suggestion that the emetic can be harmful in Gramoxone can be rebutted for other reasons.

Rebuttal

1. The data in Appendix 1 shows that the emetic is less acutely toxic than PQ.
The ratio of PQ to emetic in Gramoxone (20% PQ + 0.05% emetic) is 400 : 1.

A toxic dose of Gramoxone is approximately 15ml Gramoxone contains 7.5mg emetic.

For a 50kg man this represents $\frac{7.5}{50} = 0.15\text{mg/kg}$ as an emetic dose

for man in presence of a toxic dose of PQ.

Clearly this is at least one thousand times below the oral LD50 values of emetic to mouse and rat (Appendix 1).

2. The presence of emetic causes patients to vomit.
This reduces the amount of paraquat in the stomach and reduces the amount available for absorption into the blood. This is clearly shown in experiments with vomiting species of animals, viz dog and monkey (Appendix 2), where the presence of emetic caused a reduction in paraquat blood levels and in mortality.
Confirmatory data has been obtained from Japan [Kawai et al (1980). Nippon Noson Igakkai Zasshi, 29, 546 - 547].
Kawai et al found that the amount of paraquat eliminated by vomiting was 61 - 86% of the orally administered dose in dogs. In the group of dogs given PQ only, the blood level averaged 44mg/litre; in the group given paraquat and emetic, it was 0.26mg/litre.
It is thus quite wrong to suggest (as Prof Naito has done) that the emetic "might" increase the absorption of PQ.
3. There is substantial evidence that those people who ingest a relatively small quantity of Gramoxone and die, usually do so from lung toxicity and respiratory failure. This is typical of PQ poisoning and well documented.
Those who ingest a small quantity of Gramoxone and recover have not shown any adverse clinical or other effects in follow up medical examinations [M Yamashita et al - paper to be presented in Brussels, Aug 1986].

There is no evidence of cardiac toxicity or complications in these two groups of patients. This is acknowledged by the Misawa group.

4. Thus we are concerned with that group of people who ingest a large amount of Gramoxone and would inevitably die from PQ poisoning!

However it is also well documented that people who swallow large amounts of PQ die from multiorgan damage (kidney, liver and adrenals mainly) and in many cases shock and cardiac arrest. Although the lung may show damage, patients die before the classical symptoms of pulmonary fibrosis develop.

Thus ECG changes and toxic myocarditis following, or together with, multiorgan damage was often a feature of cases involving large PQ doses before the emetic was introduced.

eg. Malone, Carmody & Keogh (1971). Paraquat poisoning : A review of 19 cases. J. Irish med. Assoc. 64, 59 - 68

Bullwant (1986) Accidental Poisoning by Paraquat : Report of Two cases in Man. Brit. Med J. 1, 1272 - 1273

Galloway and Petrie (1972). Recovery from severe paraquat poisoning. Postgrad. Med. J. 48, 684 - 686.

Guyon, Bismuth, Lecler et Dauchy (1974)
Intoxication massive par le paraquat mortelle en moins de 24
heures Donnees toxicologiques et anatomocliniques, in J.
European de Toxicologie, 7 (No 3), 182 - 187.

Tsutsui, Nakabayashi, Suzuki and Ogura (1976)
Studies on the toxicity of paraquat - part 1. Nippon Noson
Igakkai Zasshi, 25, 614 - 621.

Thus autopsy of patients who died from large doses of Gramoxone before
the introduction of emetic often showed heart damage due to paraquat.
In the present situation it would be impossible to attribute heart
damage, in more recent autopsy cases, to emetic - and in any case quite
irrelevant.

[In their own experiments on rats and rabbits Misawa et al acknowledge
that PQ itself has an effect on the cardiovascular system.]

5. Detailed histological examination of hearts removed from dogs and
rats treated with emetic for 90 days (1.5mg/kg in dogs and 5mg/kg in
rats orally) did not show any pathological signs.
[ICI Pharmaceuticals Div. Report 3B.1/9 (July 1970)]
Thus it seems unlikely that 0.15mg/kg emetic in man as a single dose
will cause any severe effects on the heart.

17/3/86
AC/js

Appendix 1

Acute Toxicity

LD50 Values (mg/kg)

| | PP796 (Emetic)* | PQ |
|----------|-----------------|-----------|
| Rat | 150 - 155 | 100 - 110 |
| Mouse | 300 - 310 | 38 |
| Rat (iv) | 60 | 21 |

* Ref. ICI Pharmaceuticals Div. Report, 3B. 1/9 (July 1970)

Toxic dose Gramoxone approx 15ml

Emetic concentration 0.05%

15ml Gramoxone contains 7.5mg emetic

7.5

For a 50kg man this represents $\frac{7.5}{50} = 0.15\text{mg/kg}$

50

Appendix 2

The emetic Action in Reducing Paraquat Plasma Levels and Mortality in Dogs and Monkeys

1) Peak PQ Plasma Levels (ug/ml)

| | PQ alone | PQ + emetic | Reference |
|--------|----------|-----------------|------------|
| Dog | 12.5 | 1.4 (0.5mg/kg)* | CTL/T/2471 |
| | 12.5 | 0.58 (3.0mg/kg) | |
| Monkey | 18.1 | 1.6 (2.0mg/kg) | CTL/R/391 |
| | 9.6 | 2.7 (2.0mg/kg) | |

* Figs in brackets refer to dose of emetic

2) Mortality Data

Tests on monkeys and dogs have shown that the presence of emetic can reduce the toxicity of paraquat, thus

Oral LD50 (mg/kg)

| | Paraquat alone | Paraquat plus emetic (2-3mg/kg) |
|--------|----------------|---------------------------------|
| Dog | 20 - 30 | 100 |
| Monkey | 60 | 350 |

Data from CTL/R/391 Nov. 1976

DISCUSSION WITH PROFESSOR M YAMASHITA AT THE INSTITUTE OF
CLINICAL MEDICINE, UNIVERSITY OF TSUKUBA

12 March 1986

A Calderbank
Y Ohno

Background

Professor Yamashita spent 3 years at Yale University after graduating at the same Japanese University as Professor Naito, also in anaesthesiology. They came to Tsukuba together and have coauthored several papers on treatment of paraquat poisoning, potential antidotes etc.

More recently they have fallen out and gone their separate ways. Yamashita is critical of Naito and Dr Misawa (also in the same Department) and is quite friendly with ICI J.

It was he who claims that people who ingest paraquat vomit very quickly and that excessive vomiting hinders proper treatment. He has also recommended diluting the product in order to lower mortality.

Yamashita greeted us in the lobby of the building - so as to avoid meeting Naito who has an adjacent office - and we had our discussion over lunch!

Emetic

1. Y believes there may be too much emetic in Gramoxone quoting very early emesis in majority of patients and very prolonged vomiting 12 - 24 hrs later.

Asked how sure he could be about early emesis, he said he had carefully questioned patients and their relatives to arrive at this conclusion. He consults on PQ poisoning at three hospitals in the area and has been involved in the treatment of over 100 patients.

I suggested that the prolonged emesis he had observed 12 - 24 hours after ingestion was more likely due to PQ than the emetic which has a relatively short half life and its effect in animals is not prolonged (usually dogs recover within 1 hr).

2. Y normally carries out gut lavage by insertion of tube into the duodenum. Prolonged and late emesis obviously makes this procedure difficult. He discussed the possibility of using an anti-emetic drug before gut lavage.

3. On further discussion Y agreed that the emetic might be helpful in cases where a marginally toxic dose of PQ was ingested - but most people were taking larger quantities of Gramoxone. He believed that 10ml or more of a mouthful (40ml) could very quickly slip down into the duodenum before sufficient emetic was absorbed to cause its effect.

Unfortunately, because of confidentiality we were unable to discuss value of emetic in more dilute product (Preeglox-L).

4. Y was very critical of Misawa experiment as being unscientific and was surprised it was to be published in Vet & Human Toxicology Journal.

He claimed that he first suggested to Naito that the emetic might "stimulate" B-receptors (anti B-blockade) and hence increase heart rate and that N stole his idea and had Misawa et al do the experiment.

He pointed out that experiments needed to be done with the emetic alone, but fully agreed that effects, if confirmed, were irrelevant in presence of large amounts of PQ. Nevertheless he thought ICI should do some experimental work to confirm that the emetic was not causing any additive effects on the heart at lower doses of PQ.

Visit to Brussels (August 1986)

Y will be attending the XII International Congress of the European Association of Poison Control Centres, to be held in Brussels, 27 - 29 Aug 1986, and ICI J has agreed to provide his passage.

He will be presenting a paper - summary attached - which describes the follow-up (6 months to 6 years) of 40 patients who have recovered from PQ poisoning.

The paper was translated into English by ICI J translator and it is obviously quite a useful and helpful study since no after effects were recorded.

We discussed the implications - re emetic toxicity (or lack of). In early stages of poisoning raised Plasma enzyme levels (eg GOT) almost certainly due to liver damage.

Only slightly raised LDH in some patients.

He will emphasise this in paper.

During his trip to Europe Y would like to visit the Poisons Centre (New Cross Hospital) and CTL. This would be most convenient Monday & Tues following the Conference (1 - 2nd Sept). He would be accompanied by one colleague.

This would be a good opportunity to lobby Y about the benefits of the emetic, especially since our intentions regarding Preeglox-L will then be public knowledge.

Other Matters

SDS Formulation. Y volunteered that he had seen many poisoning cases of people who had intentionally ingested granules. The success of the SDS formulation would depend on how well it really prevented ingestion - difficult to judge. He said that in his view dilution, whether liquid or granule, was the most important measure.

Y will be presenting a paper on the value of Chlorpromazine as an antidote to PQ poisoning at an International Congress in Toxicology in Kyoto in July. A summary of his paper has been sent to CTL. This drug was evaluated at CTL some years ago but proved to be of no value.

Y was very interested in the Addo treatment (Cyclophosphamide and dexamethazone) and thought he might have a go.

Conclusions

I found Professor Yamashita much more scientifically orientated than Prof Naito and one could have a two way exchange of views with him. [No matter what was said to Naito he continued to play the same record back.] Y could be a very valuable resource to ICI J and should be helped at every opportunity.

Recommendations

1. Visit of Professor Yamashita plus colleague to Poisons Centre and CTL for Sept 1 and 2 be arranged.
2. Visit of AC and LLS to Yamashita be arranged for mid April to discuss properties of the emetic and further animal experiments in combination with PQ which may be desirable.

It is my view that we should encourage Y to carry out such experiments rather than do them in ICI (or as well as in ICI) and we should supply him with a sample of emetic to do this work. [Although not discussed with him I suspect he would be very interested.]

Work done by Y would carry considerably more weight in Japan than similar studies done by ICI - especially since they would originate from the same Institute as Misawa.

3. Y is a very useful contact since he is influential in clinical toxicology circles in Japan and has been asked to organise the amalgamation of the two separate associations in Osaka and Tokyo to form a "Clinical Toxicological Association of Japan", expected to be inaugurated Summer 1986.

ICI J might consider a more formal arrangement (consultancy) involving a regular (say quarterly) meeting with Professor Yamashita. Can he be involved in supervising follow up of Preeglox-L poisoning cases?

17/3/86
AC/js

Circulation

[ICI J]

Mr J S Wilson
Mr A Kohli
Mr S Tanaka
Ms Y Ohno

[ICI UK]

Dr R Birtley
Dr L L Smith
Dr T B Hart
Dr P Slade
Dr J F Sanderson
Dr P Bramley
Mr D H Brooks/Mr G A Willis



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Telegram impkemix Tokyo

From : A Calderbank

To : Dr R Birtley

cc : Dr J F Sanderson
Dr L L Smith ✓
Dr T B Hart
Dr P Slade

Your ref

Our ref

Date

AC/js

19 Mar 1986

Dear Robin

Herewith please find enclosed.

1. Copy of Prof Yamashita's summary of paper proposed for presentation in Brussels, Aug 1986.
2. Copy of minutes of meeting of Socialist DIET members and 41st Citizens with MAFF on Sat. 15th March. The minutes were prepared by the citizens and translated into English - so please interpret with caution!

Publication

After several attempts it is now reasonably clear what MAFF are after. To help them deal with repeated requests for information from various anti-pesticide etc groups, they would like summaries of the PQ toxicity studies - in particular the 4 studies specifically referred to in the attached Sat. meeting notes - published in a Japanese Journal and/or in the JMPR review.

I will be discussing with Geoff how this might best be accomplished.

In the meantime it would be helpful over here if you submitted to JMPR the Ames mutagenicity study on PQ (Shirasu et al) which was commissioned by ICI(1978).

Stop press - Saito-san + a member of EPA will be attending Codex. I will be speaking to Geoff to ask him to look out for them. They will be accompanied by Takei-san (Takeda) and expressed an interest in visiting CTL and JH - possibly 28 - 29th April. This coincides with my return to UK (25th April). Will advise you as soon as proposals are firmed up - but Saito-san could pull out at last minute if a crisis occurs & he is needed to answer DIET questions.

Best wishes

A Calderbank

MEMORANDUM

FROM : S L Allen

DATE : 17 March 1986

TO : L L Smith

REF : SLA/JB

In response to the points raised by A Calderbank (Fax 17.3.86)

- 2 Data does come from the Farrell Vol III. Hearts from both rat and dog were taken for histological examination. Individual animal data is provided and can be seen to be within normal limits - there were fewer abnormalities in treated animals than in controls.
- 3 Although, discussion of other additives may cause us more problems their presence must be addressed when assessing Masawas studies. Are the formulation details of Gramoxone W and Paragreen A the same? If not, then again, the conclusions about the emetic on the basis of his study are groundless.
- 4 In the monkey study (CTL/C/700) cardiovascular effects were not specifically studied. However as 2mg PP796/100mg paraquat (as Gramoxone W)/kg reduced mortality from 8/8 (100mg paraquat/kg) to 2/8 the advantages of the presence of emetic are obvious. In addition, the two animals which did die did not vomit until 4 and 7 hours after dosing (<1 hour for other six).

Also, cynomolgus monkeys have been given 30mg/kg p.o. PP796 with no facilities. Thus, any cardiovascular changes which may have occurred with this high dose were not life threatening.

Any experiments to evaluate the possible synergistic effects of PP796 and paraquat on the heart should be performed using oral dosing on a vomiting species. Extrapolation from i.v. data is meaningless if such high plasma concentrations cannot be obtained when dosing via the oral route.

Therefore, blood pressure, heart rate, ECG should be monitored in dogs or monkeys after treatment with emetic, paraquat or emetic + paraquat (not Gramoxone W - or have a fourth group where animals are given Gramoxone W). Animals should be monitored (particularly ECG) for at least four weeks after acute oral doses and hearts examined histologically post-mortem. Accordingly any acute cardiovascular changes will be noted and, if they occur, will determine whether such an acute incident produces prolonged physiological or pathological abnormalities.

MEMORANDUM

From: Dr S Allen
Acute Toxicity Section

Date: 6 Mar 86

To: Dr C Rhodes

Copies: Dr L L Smith
Dr M Robinson

Ref: SA/JLB

RE : EMETIC IN PREEGLOX

The proposal to increase the concentration of emetic in Preeglox from 0.05 to 0.1% has raised the question whether an emetic dose of 50mg (1mg/kg) in man will cause heart muscle damage.

Detailed histological examination of hearts removed from dogs and rats treated with emetic for 90 days (1.5 mg/kg/day in dogs, 5mg/kg/day in rats, orally) has demonstrated the absence of pathological signs. Single oral doses of 0.1 - 0.8 mg/kg in dogs have no effect on heart rate or blood pressure. In the anaesthetised dog single intravenous injections of 0.1 - 0.5 mg/kg produce transient increases in heart rate and aortic blood flow and at doses higher than 0.5 mg/kg mean arterial blood pressure is reduced. Although such transient effects on the cardiovascular system are observed no cardiac damage occurs as a consequence.

Angina has been reported in two obese patients after continual daily treatment with 2 mg emetic for 4 and 6 weeks. It seems highly improbable that such a response would have induced heart muscle damage. This conclusion is supported by the supplementary observation that no more anginal responses occurred after withdrawal of the emetic even on severe exercise.

Recent studies by Noguchi et al show apparent cardiovascular toxic effects in rats administered intravenous Gramoxone. This claim must be taken in context. These workers were examining the effects of lethal doses of a complex formulation containing not only paraquat and emetic, but also surfactants, and stretching and bittering agents. No experiments used sub-lethal injections of Gramoxone or of emetic alone. Consequently the studies do not demonstrate cardiotoxicity as a result of treatment with emetic.

In the absence of any evidence of heart muscle damage due to treatment with emetic, it is difficult to assess whether synergism occurs between paraquat and the emetic or whether there are contributory effects of other formulation ingredients. It is also difficult to extrapolate the data when the intravenous route has been used. Not only does the emetic induce vomiting but also reduces dramatically the total amount of paraquat absorbed due to its ability to prolong gastric emptying time (paraquat is not significantly absorbed from the stomach). Thus rapid, high plasma concentrations of both paraquat and emetic resulting from intravenous administration is unrealistic.

Few studies have been performed with paraquat formulations but in one cynomolgus, monkeys were given a total of 2 mg/kg emetic with 100 mg/kg paraquat (Gramoxone W). No cardiotoxic effects were recorded in surviving animals. Detailed histology was not performed.

Accordingly, it may be necessary to perform some experiments using sub-lethal doses of paraquat formulation and/or emetic looking specifically for cardiotoxic effects in-vivo and histologically post-mortem.

As the emetic is a phosphodiesterase inhibitor, it is possible that it could sensitise the myocardium to the dysrhythmic effects of adrenaline and other catecholamines. The two anginal responses may have been due to potentiation of catecholamines released on exercise. However, in the anaesthetised cat intravenous administration of emetic (0.025 - 1 mg/kg) had no effect on the cardiovascular responses to intravenous adrenaline, isoprenaline or acetylcholine. In the dog 1 mg/kg (orally) after 14 days pretreatment with 0.2 mg/kg orally produces increases in heart rate, and respiration rate which are prevented by propranolol (1 mg/kg, i.v.)

Thus, it seems likely that sensitisation may occur but only after prolonged treatment with emetic. It is extremely unlikely to occur as a result of acute, oral ingestion.

Nevertheless, such exaggerated responses to catecholamines are antagonised by B-adrenoceptor blocking drugs. It may be necessary, therefore, to advise that susceptible patients be treated with B-blockers.

SANDRA ALLEN

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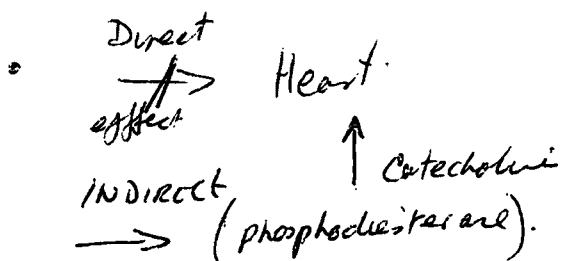
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Nevertheless, such exaggerated responses to catecholamines are antagonised by B-adrenoceptor blocking drugs. It may be necessary, therefore, to advise that susceptible patients be treated with B-blockers.

SANDRA ALLEN

What is the highest dose into an animal.

- 30mg/kg acute oral produced central sedation with recovery for 1 hr. in monkeys.
- 20mg/kg acute oral to dogs - vomiting no observed sedation.



Direct → C.N.S. → sedation
→ vomiting

Baylis
Barry Cox.

*Professor Yamashita's paper for presentation
in Brussels, Aug. 1986.*

For the treatment of paraquat poisoning such therapies as gut-lavage, DHP, plasma exchange and administration of large amounts of steroids have been attempted. Many cases so far reported ended up in death due to progressive pulmonary fibrosis even if the patients recovered from renal or hepatic insufficiency as a result of integrated administration of these therapies. Little is known as to the changes associated with paraquat poisoning in patients who were saved from paraquat poisoning. This paper reports the results of our investigations carried out on representative cases of the patients treated at Tsukuba University Hospital and Hidaka Hospital during the 1975-1985 period who were rehabilitated after recovery from paraquat poisoning following oral ingestion.

Forty cases of typical paraquat poisoning were selected for investigation out of 212 paraquat poisoning cases treated at these hospitals. All of them survived for at least six months after intentional or accidental swallowing of paraquat. Ingestion of paraquat was confirmed by interview or by positive reaction in qualitative determination of paraquat in patients' urine.

Treatments attempted on these 40 cases are summarised as follows:

- (1) Gastrolavage with a 5% Kayexalate aqueous solution was conducted. This therapy continued till there was no residue of diet in the wash.
- (2) Gutlavage was conducted for three days. A mixture of a 5% Kayexalate aqueous solution (1 litre) and a 20% Sorbitol aqueous solution (100ml) was introduced into the stomach or gut at 4-6hr intervals. The liquid was injected through

a duodenum tube inserted within the gut. When it was impossible to insert the duodenum tube due to severe vomiting, or when the duodenum tube was discharged from the duodenum to the stomach, the washing liquid was introduced into the stomach. When there was no peristalsis, acceleration of the motion was attempted by dosing of prostaglandin or other chemicals. Treatment was withdrawn from those cases in which there was no recovery of peristalsis following dosing of these chemicals.

- (3) DHP with activated charcoal was tried. The therapy continued till the urea reaction was negative. DHP-1 model (Kuraray Co.) was used for 3-10hr perfusion at a blood flow rate between 200ml/min and 300ml/min. Decision as to whether the DHP therapy should be employed or not was based on the result of qualitative determination in the urine sample collected at 10:00am on the next day, i.e. the urine collected at least 10hr after stopping of DHP.
- (4) Forced diuresis was performed through i.v. of lactated Ringer's solution and furosemide aiming at attaining urine output of 400-500ml/7hr. Forced diuresis was conducted for three
- (5) A large amount of steroids was given. The steroids used were hydrocortisone (1g) and dexamethasone (1g) and they were given for 3-7 days.

(6) Haemodialysis was performed when there was renal insufficiency and BUN and Cr were over 100mg/dl and 10mg/dl respectively or when the patient was anuric.

(7) The amount of transfusion dosed and the electrolytic balance were adjusted or corrected where necessary. The IVH-based nutrition was performed till the patient could ingest nutrients with a calorific value of at least 2000Kcal/day

Plasma paraquat determination was conducted on admission and subsequently once daily for 3-7 days. Estimation of the amount of paraquat ingested was made by subtracting the amount remaining in the container from which the patient swallowed from the initial amount of the herbicide, in those cases where the amounts of paraquat before and after ingestion were known. Estimation in other cases was through interviews with patients or patients' families. When estimating the amount of ingestion, a mouthful was assumed to be 40ml, a cupful 156ml, a Sake cupful 18ml and the amount of liquid generally poured into normal Japanese tea cup 141ml. Those patients who were conscious were asked to recite the circumstances of ingestion in order to estimate the amount taken

Chest X-P and blood biochemistry were made daily for 3-7 days. In blood biochemistry, GOT, BUN, GPT, creatinine and other values were studied.

In addition, some symptomatic treatments were carried out.

Follow-up of patients

Chest X-P were taken for all paraquat poisoning cases treated at these hospitals during Sept 85 - March 86. In addition, data on interview, lung CT scanning, lung function tests including arterial blood gas analysis, %DLco, FVC, FEV 1.0 and VC and blood biochemistry examinations conducted on these cases were available. The 40 patients studied in this investigation were asked to revisit our hospital 39 days after they had left. On revisit, they were interviewed and their chest X-P were taken. In addition, blood biochemistry was conducted on these people. BUN, Cr, GOT/GPT values over 30mg/dl, 2.0mg/dl and 100 unit respectively, were assessed as being above normal limits. In the interview, patients were asked if they had any changes in general condition, if they got easily tired, if they felt any difficulty in breathing and if they suffered from dropsy when compared with their conditions before the incident of paraquat poisoning.

Results

A total of 212 paraquat poisoning cases were treated in a ten year period at these hospitals. Of them 40 survived poisoning. The patients included 124 male and 88 female patients. (average age 40 ± 6.1 , males 41 ± 6.2 , females 42 ± 9.2 with the youngest 16 and the oldest 72) and the survivors included 12 males and 28 females (average age 32 ± 2.3 , males 33 ± 1.2 and females 30 ± 8.7).

The amount of paraquat ingested by these patients estimated by the method described before was mean 40 ± 12 ml with the largest amount being 250 ml and the lowest 5 ml and the corresponding values shown by the survivors were mean 13 ± 8.5 ml with the largest 35 ml and the lowest 5 ml. Plasma paraquat concentration determinations on admission were conducted for 180 out of 212 patients. In the case of the survivors, the determinations were conducted for 30 patients. The relationship between time to blood sample collection and plasma paraquat concentrations for fatal cases is given in Fig 1 and that for survivors, in Fig 2. The signs associated with paraquat poisoning at the early stage included vomiting, dysphagia, oropharyngitis and haemoptysis and the incidences of these signs are given in Table 2.

The average period of patients' hospital stay was 34.8 days with the longest being 65 days and the shortest 10 days. No chest X-P taken on admission showed images suggestive of development of pulmonary fibrosis. All the values obtained in biochemistry on admission including BUN, Cr, GOT, GPT, LDH and TB were within the normal limits. Renal function tests on admission revealed that 35 cases had higher BUN and Cr values, of which 12 cases were normal within 5 days, and the remaining 15 cases showed persistent higher BUN and Cr values for at least 5 days, and there were no cases with signs of anuria.

The highest values recorded in the 15 cases showing persistent higher BUN and Cr values were 100mg/dl for BUN and 5.3mg/dl for Cr. There were 13 cases in which no higher BUN and Cr values were recorded.

The liver function test showed that there were 22 cases in which no higher values of GOT, GPT, LDH and TB, 10 cases with slight increases less than 100 units of LDH and TB and 8 cases with remarkable increases over 100 units of GOT and GPT. Of the 8 cases, the highest GOT value was 1,050 units and the highest GPT, 1,120 units.

There was one case showing abnormal images in the chest X-P taken immediately after admission. There were shadows in the lower lung field of the right lung in this case. In addition cyanosis was seen and this patient was considered as having ingested the vomit accidentally. No other abnormalities were seen, and the arterial blood gas analysis showed no abnormal PaO₂, PaCO₂, pH and BE values.

Investigations conducted during _____:

[Information on general conditions]

No patients complained of weakness, dropsy, weight loss or any other abnormalities. All of the 40 cases investigated showed no specific changes associated with paraquat poisoning after recovery. Nobody suffered from difficulty in breathing during work.

The values recorded for GOT, GPT, ALP and LDH for these cases were all within the limits considered as 'normal'.

In renal function test and haematology, the values recorded for these cases (BUN, Cr, Na, K, Cl and RBC, WBC, Ht, Hb) were all within the limits considered as 'normal'.

In arterial blood gas analysis, the values recorded for all of these cases were again within the normal limits.

In lung function test, there were 3 cases in which lower %DLco values (67, 70 & 57%) were recorded. However, there were no abnormal values in the FEV1% and vital capacity.

Incidentally, none of the 40 cases had ever developed renal insufficiency, hepatic insufficiency or alcoholism.

Corresp. last year.

PS11/3



ICI Japan Limited

Mr N G E Geach
FEP
Plant Protection Division
Fernhurst

Central PO Box No 411
Tokyo 100-91 Japan

Telephone 211-6661/9
Telex 0222-2381 (2222381 ICITOK J)
Telegram Impkemix Tokyo

Your ref

Our ref

Date

FS/kya

20 Sept. 1985

Prof.'s Naito & Yamashita
University of Tsukuba

Thank you for your telex of 16 Sept. regarding our proposal for an invitation of Prof. Naito to the UK in January in place of our offer of ¥1 million.

We have now received Prof. Yamashita's study programme for a follow-up survey of survivors after PQ poisoning as referred in my visit report on 30 September.

Because of the delicate relation between the two professors it is important for us to keep a cautious balance in dealing with both of them, and we would like to make the following suggestions.

Professor Hiroshi Naito

Takeda and Nichinq agree to us that an invitation to the symposium at the Guys Hospital plus one day each to CTL and Jealott's Hill is a good way of maintaining our contact, provided the symposium is the one favoured by ICI.

We would like to know whether any person in ICI is involved in the symposium, and whether you can find any other doctors from Japan attending to it. If it is a good symposium, it might be a good thing for us to invite some other Japanese doctors, who are more friendly to us, together with Prof. Naito. I would like to know your comments.

20 Sept. 1985

Professor Mamoru Yamashita

You said in your telex of 9 September that Dr Hart is not in favour of collaboration with Prof. Yamashita's study as well as Prof. Naito from a medical view point.

From our amateur view point his study may have some value to us if he can prove that there is no after effect when recovered from PQ poisoning. We would like to know why Dr Hart is against the study.

We feel that we should give Prof. Yamashita about equal support with that we are intending to give to Prof. Naito because of the delicate balance as mentioned above. He said his study will cost ¥3.5 million, but he might be able to do with ¥1 million by using the health insurance scheme and his own car for transport of the patients. He also wishes ICI assist him with the airfare for his attendance to the first-aid medical conference in Sweden next year where he likes to report the study.

Brussels

Our recommendation is to give Prof. Yamashita ¥1 million and to consider the airfare at a nearer time when the result is known.

We look forward to receiving your advice.


F Suzuki

cc : Mr D F Manning
Mr P Slade
Dr T B Hart
Dr L L Smith

Mr Y Miyashita
Mr J S Wilson
Mr A Kohli
Mr S Tanaka
Miss Y Ohno

*Mr. Fortunately the wrong
decision was made opposite
Yamashita & his proposal.
- my view! AC*

Paraquat Poisoning: Purpose of Study

Mamoru Yamashita,
Clinical Medicine,
Tsukuba University

Typical symptoms of paraquat poisoning include ulcers in the mouth, renal and hepatic insufficiency, pulmonary oedema and pulmonary fibrosis when the compound is ingested orally. In some cases, the ulcers in the mouth could cause an extensive damage to the mucous membrane in the mouth which sometimes could be serious to affect the substratum of the mucous membrane. Yet, ulcers in the mouth are generally considered not fatal. Renal and hepatic insufficiency following paraquat ingestion are reversible within several weeks in many cases. Damages to the lungs in paraquat poisonings could induce pulmonary oedema immediately after paraquat ingestion in severe cases which would be represented by serious toxic symptoms and be fatal. In some cases, patients poisoned with paraquat could die from pulmonary fibrosis which sometimes develop after disappearance of lesions in the liver, kidneys or other organs. The onset, clinical details and prognosis of renal and hepatic insufficiency and pulmonary oedema have been reported elsewhere since these lesions would show a rapid progress. However, no works on clinical details and prognosis of pulmonary fibrosis in humans have been reported since this lesion is often shown as chronic symptoms. The prime object of our proposed study is to investigate any changes in the lungs as aftereffects of paraquat poisoning lingering for several years by carrying out follow-up surveys of patients who recovered from lung damages by the compound. The data on such investigation would contribute towards a correct judgement as to whether any aftercare should be given or not.

Studies so far carried out

- 1) M. YAMASHITA & K. NAKAMURA: Efficacy of gut lavage in the removal of paraquat in the dog; Vet. Hum Toxicol 24: 157, 1982.

On the assumption that gut lavage could be effective in treating paraquat poisonings since the therapy was demonstrated as effective in the work, it was administered in human victims. This therapy is now used in many hospitals and clinics worldwide and some doctors are regarding gut lavage the primal therapy in treating paraquat poisonings.

Incidentally, our study demonstrating efficacy of gut lavage in 94 cases of paraquat poisoning was presented at the 6th Acute Poisoning Symposium. The proceedings of the symposium is available from the Society of Agricultural Chemical Industry (Japan).

- 2) M YAMASHITA & S TAKAGI: The effectiveness of cation exchange resin as an adsorbent of paraquat both in vitro and in vivo; Vet. Hum Toxicol 25: 34, 1983.

The result of this study suggests that administration of Kayexalate would be more effective than that of bentonite since the adsorption capability of Kayexalate is approximately ten times as high as that of bentonite, although it has been considered that bentonite is the best adsorbent for paraquat. In actual, the result of this study is reflected in an extensive use of Kayexalate in treating paraquat poisoning cases. In Japan, in particular, Kayexalate is now used in almost all paraquat poisoning cases as an adsorbent.

- 3) M YAMASHITA: Toxic symptoms and treatment of acute paraquat poisonings; Emergency Medicine 30: 399, 1980.

This paper discusses the toxic symptoms of paraquat poisoning based on the author's experience of paraquat poisoning.

The scope of our studies so far conducted extends from studies of toxic symptoms based on the clinical details of many paraquat poisoning cases to exploration of effective treatment methods as described. We have succeeded in saving 38 patients out of 120 treated at our hospital by utilising the results of our studies.

Outline of the planned follow-up survey:

The patients (38) who have rehabilitated will be contacted and various investigations would be made on these patients to know the presence or absence of aftereffects of paraquat poisoning in their lungs.

Investigations to be made:

- 1) preliminary examination
- 2) lung function test and lung CT scanning
- 3) biochemical examinations of the liver and kidneys



ICI Japan Limited

FACSIMILE

FROM : A Calderbank

Signature

TOKYO OFFICE
FAX NO. 03-213-7175

TO : Dr L L Smith, CTL

OUR SRL NO /

COST CODE 43201

PAGE 1/2

DATE 17 Mar 86

REF.

COPIES : Dr J F Sanderson/Dr T B Hart, PPD Fernhurst
Dr R Birtley, PPD Fernhurst

TEXT

Dear Lewis,

Many thanks for your fax about the emetic.

The following points emerge.

Emetic in Preeglox (Dr S Allen)

1. In our present defence we have to defend emetic in Gramoxone, not in Preeglox, since only the Ministry yet know about our intention to introduce Preeglox.
2. Does the data to substantiate the second paragraph of the memorandum (6 March) come from Farrel Vol III where in the dog and rat 90 day studies heart was taken for examination. There is no comment on the heart tissue which is interpreted to mean that it was examined and found to be within normal limits.
3. 4th Para-Regarding Misawa studies we might be digging a bigger hole for ourselves if we start talking about the other additives in Gramoxone.
Incidentally no bitrex - yet.
4. Have we got a reference to support the statement about monkeys - para 6?
5. I support the first para page 2.
6. Did you notice (Pharms Report P9) how toxic the emetic is to rabbits!
Since you will be away most of May I suggest a visit from you in April would be appropriate.

An immediate agenda would be

1. Emetic and paraquat. Evaluation of possible synergistic effect on the heart.

Discuss possible experimental work. Where the work is done.

2. Visit to Professor Yamashita

To discuss (i) item (1) above and properties and value of emetic.

(ii) His paper for Brussels

(iii) Antidote research - chlorpromazine,
Addo's method.

3. Clarification of acute tox tests on PQ/DQ formulations, IET and CTL.

4. Discussion of Pharmacokinetic results - a separate fax on this subject will follow.

Since I expect to leave for UK on 25 April would you advise convenient date for your visit in order to organise item 2.

Best wishes.

A Calderbank

1/3
ICI Japan Limited

FACSIMILE

FROM : A Calderbank

Signature

*A Calderbank*TOKYO OFFICE
FAX NO. 03-213-7175TO : Dr R Birtley
PPD Fernhurst

OUR SRL NO /

COST CODE 43201

PAGE 3

DATE 13 Mar 86

REF.

COPIES : Dr J F Sanderson/Dr P Slade, PPD Fernhurst
Dr L L Smith, CTL

TEXT

PLEASE NOTE TRANSLATION OF ARTICLE WHICH APPEARED IN LOCAL
NEWSPAPER ATTACHED RELATING TO MISAWA WORK.

JUST LEARNED MISAWA IS TO PUBLISH HIS STUDY ON THE EMETIC IN
VETERINARY & HUMAN TOXICOLOGY.

THE NEWSPAPER ARTICLE HAS PRECIPITATED QUESTIONS FROM MAFF HQ
RELATING TO PQ TOXICITY DATA TO BE SUBMITTED FOR JAPAN RE-
REGISTRATION AND COMPARISON WITH DATA SUBMITTED (OR TO BE
SUBMITTED) TO JMPR.

CONCERN HERE WITH FINAL SENTENCE ON PQ JMPR 1985 REPORT.
REQUIRED 1986 : "SUBMISSION OF ALL DATA AVAILABLE FOR COMPLETE
RE-EVALUATION". HENCE MY CALL LAST EVENING.

UNABLE TO CONTACT GEFF. HOWEVER WILL CONCOCT RESPONSE WHICH
I BELIEVE REASONABLY ACCURATE.

FURTHERMORE QUESTIONS IN DIET ABOUT PROGRESS ON MAKING PQ SAFER
HAVE ADDED TO URGENCY OF RESPONSE AND LABOUR PARTY ARE ASKING
FOR DATA DISCLOSURE ON PQ FROM MAFF. I BELIEVE WE CAN GO
SOME WAY TOWARDS MEETING THIS REQUEST.

ALSO REQUEST TO REBUTT MISAWA WITH TECHNICAL DATA MORE URGENT.
LETTER WITH FULL DETAILS TO FOLLOW.

REGARDS.

A CALDERBANK

2/3

Dangerous "Danger preventing method" - a Tsukuba University study shows "Paraquat" incorporating emetic could cause heart injury

A study using experimental animals carried out by a group of researchers led by Prof Shogo Misawa (48) (forensic medicine), Community Medicine Dept, Tsukuba University, showed that an emetic incorporated into some paraquat herbicide for the purpose of preventing risk of paraquat following accidental swallowing could be a causative substance in acute death rather than preventing danger by this herbicide. The addition of emetic to paraquat herbicide is obligatory under rules issued by Ministry of Agriculture, Forestry and Fisheries, but the group of researchers conducted the study advocate pursuit of other methods for preventing risk of paraquat.

The study shows that fatal cases of paraquat poisoning which amounted to 1,300/year by the latest statistics are broadly categorised into two groups; those which ended up in death within several hours to one or two days and those which died after about one week. It has been known that the cause of death in the second group is pulmonary fibrosis, but that for the first group is unknown.

Prof Misawa and his group investigated the potential effects on the heart and lung functions of emeticised paraquat, non-emeticised paraquat and pure paraquat solution which were dosed iv to rats, using rat electrocardiography and respiration data. The rats receiving emeticised paraquat showed cardiac arrest following reduction in the function of the sinus node in the right atrium approximately 20 seconds after injection, although the animals showed regular respiration for approximately 10 seconds following cardiac arrest. The rats receiving non-emeticised paraquat or pure paraquat solution both showed arrest of respiration first and then cardiac arrest following showing signs of anoxia. Similar results were obtained in experiments using rabbits.

Prof Misawa and his researcher-group consider, based on the results of their experiments, that the emetic incorporated into paraquat could give damage to the heart before the lungs are affected by toxic effects of paraquat.

Prof Hiroshi Naito (54) (Anesthesiology), Institute of Clinical Medicine, Tsukuba University, who represents "Poison 110" and has partly participated in the study of Prof Misawa et al as a researcher having expert knowledge of poisoning studies contends that "the addition of emetic could cause adverse effects" on the ground that the emetic itself is an unnegligible toxin and it may enhance absorption of paraquat by the body.

Reduces. X

Told officers of the Plant Protection Division, MAFF, on receiving the information: "Exclusion of the emetic would probably induce a more intensive absorption of paraquat since the emetic would encourage vomiting. Anyway, we would obtain the data on their study to investigate their points."

- Yomiuri Shimbun, 11.3.86 (Evening issue) -



ICI Japan Limited

FACSIMILE

FROM : A Calderbank

Signature
A Calderbank

TOKYO OFFICE
FAX NO. 03-213-7175

TO : Dr R Birtley
PPD Fernhurst

OUR SRL NO

COST CODE 43201

PAGE 2

DATE 20 Feb 86

REF.

STAN CHART.

COPIES : ~~Dr J F Sanderson, PPD Fernhurst~~
Dr J F Sanderson, PPD Fernhurst
Dr P Bramley, " "

PPD -

*Att. Au Report at PPD
on it.*

TEXT

Emetic in Preeglox

In order to prepare myself for possible questions in (a) Supporting MAFF opposite Prof Misawa and (b) in supporting an increase 0.05 to 0.1% emetic. I would appreciate comments from Lewis on calculations below party taken from his note to JTB.

1. 10 ml Gramoxone (20% containing 0.05%) is perhaps below an LD₅₀ and hopefully man will survive without any effects from emetic ingested (5mg or 0.1mg/kg body wt).
2. Similarly 50ml Preeglox (4.5% PQ + DQ and 0.1%) may approx. to an LD₅₀ dose.
Emetic ingested would be 50mg or 1.0mg/kg body wt
3. Can we be sure this amount of emetic will not cause heart problems in man?
4. Helpful evidence is virtual NEL in dogs (1.5mg/kg) and rats (5mg/kg) over 90 days - however no indications of any cardiovascular involvement.
5. Yet Misawa et al are getting cardiovascular effects on rats (and rabbits) at iv levels of 0.14mg/kg, equivalent to about 0.42mg/kg orally.
6. Man is stated to be more sensitive to emetic properties than dog, monkey and rat.
7. Doses of 2mg to man for 4 and 6 weeks caused angina in two patients. This is equivalent to 0.04mg/kg.

8. The question is can we be really confident that a sub-lethal dose of Praeglox (with 0.1% emetic) viz 50ml with a single shot of 50mg (or 1.0mg/kg) will not cause heart muscle damage.

The maximum dose of emetic previously given to man (Pharms clinical trial) was 8mg (0.16mg/kg).

Is there any way - or arguments to make us more confident?

9. One can certainly criticise the Misawa experiments.

To be meaningful he should have tried to demonstrate a cardiovascular effect using sub-lethal injection of Gramoxone, or tried the effect of emetic alone (I suspect he didn't have any).

Nevertheless the effects he is getting at the equivalent of 0.42mg/kg do not tie up with the Pharms 90 day rat expt.

One has to assume there is a synergistic effect between PQ and the emetic. If this is so what happens if you increase the emetic level with sub-lethal doses of PQ?

Sorry for this rambling but I would appreciate comments (helpful!) from the expert.

Regards

A Calderbank



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Tokyo 100-91 Japan

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Telex 0222-2381 (2222381 ICITOK J)
Telegram impkemix Tokyo

From : A Calderbank

To : Dr R Birtley

cc : Dr J F Sanderson
Dr L L Smith
Dr T B Hart

Your ref

Our ref

Date

AC/js

21 February 1986

Dear Robin,

Emetic/Preeglox

Following my recent faxes on this subject.
Am still worried about emetic level (0.1%) proposed for Preeglox.
I will try to summarise my concern and be prepared to be shot
down by the experts.
Furthermore I need rebuttal of these concerns in order to assure
others.

1. Misawa et al report cardiovascular effects (rats & rabbits)
brought about by Gramoxone (+emetic) but not by Paragreen
(no emetic), nor by paraquat alone.
There effects were produced by iv injection at several times
the lethal dose of PQ, nevertheless the amount of emetic
involved (at 0.05%) was 0.14mg/kg iv (equivalent to about
0.42mg/kg orally?).
It may be the iv injection (of emetic) gives a sudden high
level in blood which is unrealistic in practice.
2. No cardiovascular effects have been recorded with rats or
dogs in the Pharms 90 day studies up to levels of emetic of
5mg/kg and 1.5mg/kg respectively.
3. According to Table 1 in Rose's report CTL/R/390 man is much
more sensitive in vomiting response to the emetic than monkey,
pig or dog.
From the limited data in man there seemed to be a good
vomiting response at about 0.1mg/kg or a total dose of 8mg.
This is the max. amount given to man.
The emetic was given in tablet form and Rose believed the
rate of absorption, which is related to the onset of emesis,
would be faster from solution.

4. The ratio of PQ to emetic in Gramoxone is 400:1. In Preeglox (with 0.05% emetic) it will be reduced to 90:1. 50ml of Preeglox (4.5% PQ + 4.5% DQ) will provide a dose of PQ close to the LD₅₀ for man. If it were to contain emetic at 0.05%, this would amount to a dose of 25mg emetic or approx 0.5mg/kg for a 50kg man.

It can be argued from the data already in the hands of the authorities that this amount should be more than adequate to give a good vomiting response. Especially since the volume of more dilute formulation left in the stomach as less likely to constitute a toxic dose. Consuming larger volumes (normally lethal) of Preeglox would ensure correspondingly larger amounts of emetic and hence even st more rapid emesis when mo needed.

5. Doubling the emetic level will induce an even faster response but is it really necessary and can we be sure this level of emetic will be safe to those who would normally recover? (ie 50ml volume)

We would be providing doses of emetic of 1mg/kg and above close to maximum levels given to animals. Since man is more sensitive to emesis he may be more sensitive to other properties of the emetic.

Angina has been reported by two subjects given 2mg or 0.03mg/kg for several weeks.

6. Returning to the alleged cardiovascular effects of the emetic.

Since no cardiovascular effects have been recorded for dogs and rats in the Pharms studies one wonders about a synergistic effect in presence of PQ.

7. PQ poisoned patients have been reported with ECG abnormalities - did this happen before emetic was introduced? Certainly patients taking large doses of PQ have died from cardiovascular collapse and heart failure.

8. I seem to remember that some of the earlier Pharms β -blocker heart drugs caused bronchial constriction. The emetic acts as a bronchial dilator and I am perhaps asking a naive question as to whether the emetic might have the reverse effect to a β -blocker and stimulate noradrenaline production or action on the heart muscles.

9. All this causes me to ask whether it is considered desirable to do one or two more animal experiments before implementing the increased emetic level. If I don't ask the question someone else might!

I would suggest - again perhaps naively and having seen only two of Lewis's four reports - that a further experiment on dogs might be performed using sub-lethal doses of PQ with and without emetic and monitor with ECG any effects on the cardiovascular system.

I trust these notes transmit my concern and hopefully the answers provided will help me counter criticism of the need to double the emetic level and also the allegations of Misawa etal that the emetic is likely to be harmful to man.

Yours sincerely,

Alan

A Calderbank



ICI Japan Limited

FACSIMILE

FROM : A Calderbank

Signature

TOKYO OFFICE
FAX NO. 03-213-7175TO : Dr R Birtley
PPD Fernhurst

OUR SRL NO 2

COST CODE 43201

PAGE 1/3

DATE 25 Feb 86

REF.

COPIES : Dr J F Sanderson, PPD Fernhurst
Dr L L Smith, CTL

TEXT

DQ/PQ/Preeglox - Acute tox tests CTL and IET

In response to your fax Feb 24.

Plan is to submit registration package for Preeglox 27 March.

1. This will contain MSRL data for the basic oral, dermal LD50 and skin and eye irritation and sensitisation. A report of a visit made to MSRL yesterday attached.
2. IET data on influence of DQ on PQ toxicity to be submitted. Preliminary data will be available for submission 27/3. Full report containing pathology will follow.
3. Duplicate work at CTL (acute toxicity of formulations) will not be submitted but will be held in reserve as insurance in case there are problems with the IET data.
4. The CTL radioactive expt. (pharmacokinetic) will need to be submitted. MAFF are aware it is being done and are interested in the outcome. Would appreciate receiving a draft version of this report so that translation can be proceeding as you suggest. Any alterations can easily be made later. Appreciate letter report earliest in order to translate & include in submission.
5. Would also appreciate draft of CTL acute tox study report. Despite lack of extra doses it would be useful to have the report here to expedite matters if it is decided later there is a need to submit.

Thanks and best regards.

A Calderbank

Visit to Medical Scientific Research Laboratory (MSRL)
Feb 24th 1986

by Dr A Calderbank and Mr T Shigeno

Small laboratory on outskirts of Oomiya-City, Saitama Pref.
Total staff approx 40.

President : Seiji Yoshida (Mr)
Study Director : Yukio Sugiya (Dr)

Although they have nine barriered units (each taking about 400 rodents) for chronic studies, the laboratory seems relatively unsophisticated and could not be recommended for any long term studies.

The staff seemed competent and dedicated and we have little doubt that the handling of acute studies is done adequately and well.

Data is recorded manually and later put into a computer.
Histopathology reading of slides mainly contracted out.

Studies are carried out to GLP standards and they have an independent Quality Assurance Unit. They were recently inspected by MAFF and we were told everything went well - the laboratory hopes to get a favorable certificate shortly.

Progress of ICI Studies with Preeglox

Rat and Mouse oral (emetic 0.05%)

Remaining animals sacrificed 19/20 Feb.
Data presently being recorded and analysed.
Preliminary figures given to us suggest an LD50 in both species of about 2,000 - 2,400mg formulation/kg which would give a figure of around 100mg/kg PQ ion.

Stressed that MSRL should include a statement of the volume (dilution) of the formulation which was dosed.

Rat dermal : An LD₅₀ > 2,000mg formulation/kg recorded.
Data in preparation.

Rabbit skin and eye irritation

Marked effects of the neat formulation noted shown by good photographs.

Eye with irrigation, better than without, and showing recovery after an extended period of observation (21 days). Reports which will contain photos were being QA'd.

Skin irritation still showed marked erythema after 14 days but looked to be recovering.

Skin sensitisation (g.pigs)

Usually dose is arranged so as to obtain all zeros in negative control animals (ie no sensitisation) avoiding need to subtract from fully treated (sensitised) animals.

Expt. started 18/2. Due to finish 14/3 and to be reported 26/3 - Very tight!

Rat + Mouse oral & Rat dermal (0.1% emetic)

Results due : dermal (27/2), rat oral (13/3), mouse oral (27/3). Reporting 10/4. The president (Mr Yoshida) agreed to try to get the schedule speeded up.

25/2/86
AC/js



FACSIMILE

FROM : A Calderbank

ICI Japan Limited

TOKYO OFFICE
FAX NO. 03-213-7175

**TO : Dr R Birtley
PPD Fernhurst**

OUR SRL NO

COST CODE 43201

PAGE 1/2

DATE 25 Feb 86

REF.

**COPIES : Dr J F Sanderson/Dr P Slade/Dr P Bramley
PPD Fernhurst**

Dr L L Smith, CTL

TEXT

Emetic in Preeglox

Attached is a brief proposed to submit to MAFF along with the Preeglox-L petition.

I have been careful to avoid mentioning the concentration of emetic so that we could later make out a case for a 0.1% level if this is agreed.

Would appreciate your comments on the text which is mostly taken from Lewis's memo to JTB.

Regards

A Calderbank

3/2

Value of Emetic in Preeglox

There is no good evidence that the presence of emetic in Gramoxone-100 (20% paraquat ion) has helped to improve survival of those ingesting the product. This is probably because the doses taken for suicidal intent, which constitute the majority of poisonings, are usually large and also the absorption of paraquat into the bloodstream is relatively fast. Even if emesis occurs within 30 min sufficient paraquat is absorbed or remains in the gastrointestinal tract to constitute a lethal dose.

Dilution (to 4.5% paraquat ion) will obviously increase the volume of formulation which contains a lethal dose (viz. to about 60 - 80ml). This means that if emesis occurs and only 50% of the stomach contents are removed it is less likely that a lethal quantity of paraquat will remain in the stomach (Compare if a mouthful (say 40ml) of Gramoxone is swallowed and 20ml vomited, a lethal dose may well remain).

Furthermore absorption of paraquat will be slower when a more dilute formulation is swallowed giving the emetic more time to cause its effect (vomiting) before a lethal level is absorbed into the bloodstream.

Thus it is reasoned that the emetic will be much more effective in reducing the mortality rate in persons who swallow Preeglox than in those who previously swallowed Gramoxone.



ICI Japan Limited

FACSIMILE

FROM : A Calderbank

Signature

TOKYO OFFICE
FAX NO. 03-213-7175TO : Dr L L Smith
CTL

OUR SRL NO

COST CODE 43201

PAGE 1/3

DATE 25 Feb 86

REF.

COPIES : Dr J F Sanderson/Dr R Birtley/Dr P Bramley/Dr T B Hart
PPD Fernhurst

TEXT

Emetic in Preeglox

Thanks for your fax Feb 24.

In the meantime I have responded to your earlier rather terse fax on same subject.

In order to brief myself regarding available human and animal data on the emetic prior to discussions with Saito-san (MAFF Headquarters) to respond to Misawa et al allegations I consulted the UK registration petition dossier (Dated 13/2/76) - the most relevant papers being.

- (a) Summary Sheets 1 + 2 dated 22.7.76
- (b) Ref 8. Rose report CTL/R/391
- (c) Ref 9. Rose report CTL/R/390

The time is clearly approaching when more detailed discussion is needed because of diverging views.
However in quick response to your points.

1. Agreed. I was trying to arrive at a dose of emetic man might get when surviving from PQ.
2. Understood. Present level (0.05%) emetic would give a dose of 25mg or 0.5mg/kg man (50kg man).
The optimum level for dog from your experiments is 3mg/kg.
According to the Rose reports man is about 10 times more sensitive to emetic properties than dog (admittedly on limited data in man). Thus the optimum level for rapid emesis in man might be extrapolated to 0.3mg/kg.

Consequently I deduce that 0.5mg/kg for man (or present level in Preeglox at 0.05%) should be adequate.

Higher volumes of Preeglox, which might be judged to be lethal, would obviously provide higher quantities of emetic and produce even faster emesis.

I agree that in these circumstances the toxicity of the emetic is of little importance - since the patient would otherwise die from PQ.

3. Mainly I agree. However the toxicity (death) due to PQ might be masking any effects due to large doses of emetic. With Preeglox man may be getting relatively larger doses of emetic and surviving (from PQ). Thus the difference in toxicity between PQ and emetic depends on their relative doses and we seem to know little about the toxicity of the emetic to man. Previously the largest dose administered to man was 0.11mg/kg and two patients given 0.03 (for a few weeks) got angina.

4. Data from emetic summary petition to UK.

5. Agreed. I was extrapolating an oral dose from an iv dose.

Possibly in both respects.

Emesis - see Rose CTL/R/390 Table 1.

Cardiovascular - No effects reported after 90 days at 1.5mg/kg.

Man reported angina after a few weeks at 0.03mg/kg. (Emetic summary report)

7. Agreed, but we don't really know the possible cardiovascular effects of the emetic to man at higher acute doses when he would normally recover from PQ.

8 and 9. I believe these questions are important but may be difficult to answer.

Most of the above concern relates to the implication that man is more sensitive to the emetic properties of PF796 than the dog, which stems from the Pharms data, and also the suggestion that the emetic might cause cardiovascular problems in man. Finally a concern that there might be synergistic effects of sub lethal doses of PQ plus emetic.

A lot of 'mights' I agree. But it would seem from previous data that the emetic level (0.05%) in Praeglox is OK. Why step further into the unknown? We do need to get it right this time.

Hope this is helpful

Regards

A Calderbank

8. L.L. Smith, A. Wright, I. Wyatt, and M.S. Rose, Effective treatment for paraquat poisoning in rats and its relevance to treatment of paraquat poisoning in man, Br. Med. J., 4: 569 (1974).
9. P.N. Bennett, D.S. Davies, and G.M. Hawkesworth, In vivo absorption studies with paraquat and diquat in the dog, Br. J. Pharmacol., 58: 284 (1976).
10. D.G. Clark, Inhibition of the absorption of paraquat from the gastrointestinal tract by adsorbents, Br. J. Industr. Med., 28: 186 (1971).
11. K. Nakamura, M. Yamashita, and H. Naito, Efficacy of gut lavage in the removal of paraquat in the dog, Vet. Human Toxicol., 24(Suppl): 157 (1982).
12. A.T. Proudfoot, M.S. Stewart, T. Levitt, and B. Widdop, Paraquat poisoning: significance of plasma paraquat concentrations, Lancet, 2: 330 (1979).
13. N. Noguchi, S. Nisawa, S. Tsuchiya, H. Yamamoto, and H. Naito, Cardiorespiratory effects of paraquat with and without emetics on Wistar rats, Vet. Human Toxicol., 27: 508 (1985).

14. A. Bramley, and T.B. Hart, Paraquat poisoning in the United Kingdom, Human Toxicol., 2: 417 (1983).
15. A.P. Denduyts-Whitehead, T.B. Hart, and G.N. Volans, Effects of the addition of an emetic to paraquat formulations on acute poisoning in man, J. Toxicol. Clin. Toxicol., 23: 422 (1985).
16. L.J. Onyon, and G.N. Volans, The epidemiology and prevention of paraquat poisoning, Human Toxicol., 6: 19 (1987).
17. C. Bismuth, R. Garnier, S. Dally, P.E. Fournier, and J.M. Scherrmann, Prognosis and treatment of paraquat poisoning: a review of 28 cases, J. Toxicol. Clin. Toxicol., 19: 461 (1982).
18. H. Naito, and A.M. Yamashita, Epidemiology of paraquat in Japan and a new safe formulation of paraquat, Human Toxicol., 6: 87 (1986).
19. P.S. Physick, Account of a new mode of extracting poisonous substances from the stomach, The Eclectic Repertory, 3: 111 (1812).
20. V. Danel, J.A. Henry, and E. Glucksman, Activated charcoal, emesis, and gastric lavage in aspirin overdose, Br. Med. J.,

PQ/Emetic, PP796Human references

X SEPTEMBER 1984 I2835B
EFFECT OF THE ADDITION OF A EMETIC TO PARAQUAT FORMULATIONS ON ACUTE
POISONING
IN MAN
T B HART A WHITEHEAD
I2835B ✓
ORAL HUMAN EPIDEMIOLOGY MORTALITY 1984

X REPORT NO. P-C I22430 JULY 1970
SUBMISSION OF EVIDENCE TO THE COMMITTEE ON SAFETY OF DRUGS PRIOR
TO THE INTRODUCTION INTO HUMANS OF ICI 63,197
ICI PHARMACEUTICALS DIVISION
I22430

For interest, other references on Toxbib

X 23 JULY 1990 S222J
TOXICOLOGICAL DATA ON PARAQUAT EMETICS
J M GROVE
S222J
EMETIC

5 JULY 1990 S221K
PP796 TOXICOLOGICAL DATA
J W BOTHAM
S221K
ACUTE DERMAL ORAL GUINEA PIG RABBIT RAT AMES EYE IRRITATION MUTAGENICITY
SENSITISATION SKIN

17 AUGUST 1989 S206J
SENSITIZATION DATA ON ADJUVANTS IN JAPANESE DIQUAT FORMULATIONS
J W BOTHAM
S206J
GUINEA PIG HUMAN RABBIT EYE IRRITATION SENSITISATION SKIN URTICARIA

VET HUM TOXICOL 27(5) 381-5 1985
EMETIC EFFECT OF TRIAZOLOPYRIMIDINE A PYRIMIDINE COMPOUND IN DOGS
F AKAHORI T ICHIMURA T MASAOKA S ARAI
1985
ACUTE ORAL

*Have post
copy -
des Jean Lantier
Néto?*
X M YAMASHITA K NAKAMURA S SATO H NAITO
THE PLASMA PARAQUAT CONCENTRATION OF DOGS ADMINISTERED PARAQUAT WITH EMETIC
VET HUMAN TOXICOL 24 SUPPL 48-49 1982

FED REG 47(72) 16022 1982 I2765H
TOLERANCES AND EXEMPTIONS FROM TOLERANCES FOR PESTICIDE CHEMICALS IN OR ON
RAW AGRICULTURAL COMMODITIES 2-AMINO-4,5-DIHYDRO-6-METHYL-4-PROPYL-S-TRIAZOLO
(1,5 ALPHA) PYRIMIDIN-5-ONE
EPA
I2765H
1982

FED REG 47(72) 16022 1982 I2765H
TOLERANCES AND EXEMPTIONS FROM TOLERANCES FOR PESTICIDE CHEMICALS IN OR ON
RAW AGRICULTURAL COMMODITIES 2-AMINO-4,5-DIHYDRO-6-METHYL-4-PROPYL-S-TRIAZOLO
(1,5-ALPHA) PYRIMIDIN-5-ONE
E L JOHNSON
I2765H
EMETIC 1982

X UNPUBLISHED REPORT NOV 1978 I2336X
PP 796 ADDED TO GRAMOXONE L. EFFECTS ON ACUTE TOXICITY IN RATS 2.
EFFECTS ON USERS 3. EFFECTS OF VARIOUS COMPOUNDS AS A POSSIBLE
ANTIDOTE IN PARAQUAT POISONING
NIHON NOHYAKU CO LTD
I2336X ACUTE OCCUPATIONAL ORAL HUMAN SPRAY

2ND JULY 1976
LITERATURE SEARCH IN CONNECTION WITH TOXICOLOGICAL INQUIRY ON ICI
65,329 FROM PHARMACEUTICALS DIVISION NO INFORMATION FOUND
RB WRIGHT
1976

2ND JULY 1976
LITERATURE SEARCH IN CONNECTION WITH TOXICOLOGICAL INQUIRY ON ICI
63,197 FROM PHARMACEUTICALS DIVISION NO INFORMATION FOUND
RB WRIGHT
1976

ICI LIMITED BRIT APPL 76/15584 P6 1976
HERBICIDAL COMPOSITION OF BIPYRIDILIUM QUATERNARY SALTS
AND EMETIC AMOUNTS OF S-TRIAZOLO PYRIMIDINE DERIVATIVES
GE DAVIES DM FOULKES
CHEM ABSTR 87(23) 178760 1977

APPLICATION TO THE LICENSING AUTHORITY FOR THE ISSUE OF AN
ANIMAL TEST CERTIFICATE IN RESPECT OF 63,197
ICI PHARMACEUTICALS DIVISION
CONTACT CTL REPORTS
ACUTE ORAL TOX RAT, ACUTE IV TOX MOUSE RAT RABBIT
ACUTE IM PIG

I2243N
APPLICATION TO THE LICENSING AUTHORITY FOR A CLINICAL TRIAL
CERTIFICATE IN RESPECT OF ICI 63,197
ICI PHARMACEUTICALS DIVISION
I2243N
SKIN TOX DOG SKIN IRRITANCY, RABBIT, GUINEA PIG, SKIN
SENSITISATION RABBIT

REPORT NO P-C VOL II JULY 1970 I2243P
ICI 63,197 PHARMACOLOGY AND BIOCHEMISTRY
ICI PHARMACEUTICALS DIVISION
I2243P

IMPERIAL CHEMICAL INDUSTRIES PLC

CENTRAL TOXICOLOGY LABORATORY

For info, CIL reports.

PP796

Reports of toxicity studies performed at CTL

CTL Report No

| | |
|------------|---|
| CTL/T/1277 | Toxicological Report: ICI 63,197. Moses SE. March 1979 |
| CTL/P/338 | PP 796: Short term predictive tests for carcinogenicity. Longstaff E. March 1977. |
| CTL/R/390 | The concentration of PP 796 required to produce emesis in experimental animals. Rose MS. October 1976 |
| CTL/R/391 | The effect of administration of an emetic (PP 796) on paraquat toxicity in dog and monkey. Rose MS, Parkinson GR, Laird WJD. November 1976 |
| CTL/R/489 | The effect of PP796 on gastric emptying in rats, mice and monkeys and on paraquat absorption in rats. Wright AF, Wyatt I and Rose MS. 19 October 1979 |
| CTL/T/2452 | PP796: Effect of stomach status on emetic efficacy in dogs. Brammer A, Robinson M. 23rd January 1986 |
| CTL/T/2451 | PP796 and TKPP: Acute toxicity studies in dogs. Brammer A, Robinson M. 19th December 1985 |
| CTL/T/2471 | PP796: Emetic study in paraquat treated dogs. Robinson M, Brammer A. 6th March 1986 |
| CTL/T/2459 | PP696: Emetic dose response study in dogs. Brammer A, Robinson M. 6th March 1986 |
| CTL// | 5H-s-triazolo(1,5-A)pyrimidin-5-one: Final short term carcinogenesis report sheet SR76204 Longstaff E, Ashby J. 6th October 1976 |

IMPERIAL CHEMICAL INDUSTRIES LIMITED
CENTRAL TOXICOLOGY LABORATORY

PP 796

Reports of toxicity studies performed at outside
laboratories

CTL REPORT NO

| | |
|--|-----------|
| The effect of 4 antiemetic substances on the emetic activity of PP 796 in cynomolgus monkeys. Purser DA et al. Huntingdon Research Centre. Report No. ICI 193/78628. September 1978. | CTL/C/575 |
| The effects of emetic PP 796 on the oral toxicity of diquat in cynomolgus monkeys. Purser DA, Grimshaw P, Cobb LM. Huntingdon Research Centre. Report No. ICI 172/78481. 28th September 1978. | CTL/C/576 |
| The toxicity of orally administered emetic PP 796 in cynomolgus monkeys. Purser DA, Grimshaw P, Cobb LM. Huntingdon Research Centre. Report No. ICI 171/78627. 8th November 1978. | CTL/C/613 |
| The effect of emetic PP 796 on the oral toxicity of malathion in cynomolgus monkeys. Purser DA, Grimshaw P. Huntingdon Research Centre. Report No. ICI/151A. 20th October 1977. | CTL/C/743 |
| The effects of emetic PP 796 on the oral toxicity of parathion in cynomolgus monkeys. Purser DA, Grimshaw P. Huntingdon Research Centre. Report No. ICI/151B. 16th September 1977. | CTL/C/746 |
| The acute oral toxicity and mode of action of emetic PP796 in cynomolgus monkeys, and its effect upon the acute oral toxicity of several formulations of paraquat. Cobb LM, Purser DA, Coombs DW & Grimshaw P. Huntingdon Research Centre. Report No ICI 119/78556 19 March 1979 | CTL/C/700 |
| The effects of emetic PP796 on the oral toxicity of ethylene glycol in cynomolgus monkeys. Grimshaw P, Purser DA & Cobb LM. Huntingdon Research Centre. Report No ICI 1292/79470. 21 Jun 1979 | CTL/C/728 |
| The effects of emetic PP 796 on the oral toxicity of Furadan in cynomolgus monkeys. Grimshaw P, Purser DA & Cobb LM. Huntingdon Research Centre. October 1979. Report No. ICI 282/79469 | CTL/C/775 |

IMPERIAL CHEMICAL INDUSTRIES PLC

CENTRAL TOXICOLOGY LABORATORY

PP796

CTL Letter Reports

CTL Report No

| | |
|-----------------------|---|
| CTL/L/1359 | PP796: Emetic efficacy in a blank paraquat formulation. Collins MA, Robinson M. 8th September 1986 |
| CTL/L/1839 | PP796: Genetic Toxicology Screening. 17th December 1987 |
| CTL/L/2034 | PP796: Acute oral toxicity to the rat. Davison VM. 10th May 1988 |
| CTL/L/2004 | PP796: Acute dermal toxicity to the rat. Davison VM. 10th May 1988 |

23/7/90
From
Miss J M Grove
Information Services Section

ICI Central Toxicology Laboratory

Alderley Park
Macclesfield Cheshire SK10 4TJ

To
Dr N Sabapathy
ICI Agrochemicals
Fernhurst

Tel: 0625 582711
Telex: 669095/669388
Fax: 0625 582897

Copies to

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|----------|-----------------|-----------------------------|-----------------------------|---------|
| Your ref | Our ref | Direct line | Tel ext | Date |
| | JMG/JC/3/52/COM | <div>Redacted - EU PH</div> | <div>Redacted - EU PH</div> | 23.7.90 |

TOXICOLOGICAL DATA ON PARAQUAT EMETICS

Enclosed is a copy of an article on the emetic effect of triazolopyrimidine (1). In addition to this there is also a pharmaceuticals report on the toxicity of ICI 63197 (2,3). Unfortunately we do not hold copies of this report at CTL but the information may be obtained by contacting pharmaceuticals division directly.

Please let me know if you require any further information.

Miss J M Grove

References

1. Akahorn F, Ichimura T, Masaoka T et al
Emetic effect of triazolopyrimidine a pyrimidine compounds in dogs
Vet Hum Toxicol 27 381-5 1985
2. ICI Pharmaceuticals Division
ICI 63,197 pharmacology and biochemistry
Report No. PH18987C Vol 11 1970
3. ICI Pharmaceuticals Division
Submission of evidence to the Committee on Safety of Drugs prior to the
introduction into humans of ICI 62,197
Report No. PH18987C July 1970

Epidemiology of Paraquat in Japan and a New Safe Formulation of Paraquat

H. Naito & M. Yamashita

Institute of Clinical Medicine, University of Tsukuba, Tsukuba, Japan

Epidemiology study

According to statistics published by the Japanese Ministry of Health and Welfare, more than 1900 people were killed by paraquat in 1985 and the number of deaths is increasing sharply (Figure 1). More than 97% of deaths due to pesticides 'other than organophosphates and carbamates' (International Classification of Diseases, Code 989.3) in Figure 1 are considered to be due to paraquat poisoning. Other causes include organochlorines, blasticidin and chloropicrin which are only rarely the cause of death. The addition of emetics and colouring agents to paraquat formulations has had no noticeable effect on mortality.

We have treated 131 patients with paraquat poisoning in our poison treatment centre in the past four years, only 39 patients survived (mortality rate 70%). Prevention of paraquat poisoning whether as a result of accidents, suicide or homicide is thus urgent in Japan as well as in other countries.

New safe formulation of paraquat

A novel non-swallowable formulation—Paraquat Water Dispersible Granule (WDR)—developed jointly by Tsukuba University and SDS Biotech K.K. is considered to be one of the promising tools for the prevention of paraquat poisoning.

Paraquat WDG contains a natural thickening agent which makes it more difficult to swallow. Even when a lethal dose of paraquat WDG is dissolved in a glass of water, milk, soft drink, wine, etc., a non-fluidizable mixture is formed. The formulation can also be made more disagreeable to take by adding a stenching agent.

Methods

The following study was conducted in order to examine the elution rate of paraquat dichloride from ingested gel when in contact with gastric or intestinal juices.

Paraquat WDG (6 g) was gelled with 35 ml of water, to this was added 100 ml of artificial gastric or intestinal juice (made according to the Japanese

Pharmacopoeia). In the dynamic study, gelled paraquat granules and artificial gastric or intestinal juice were added to a 500 ml separating funnel and shaken at approx. 50 mm amplitude 30 times/min. Temperature was maintained at 37°C in the stationary study and ranged from 20–30°C in the dynamic study. Samples (10 ml for stationary study and 5 ml for dynamic study) were withdrawn for determination of paraquat concentrations at 0 min, 10 min, 30 min, 1 h, 3 h, 6 h and 24 h after the mixing of gelled paraquat and gastric or intestinal juice. Immediately after each sampling, an equal volume of gastric or intestinal juice was added. The change in concentration due to this sampling method was corrected by calculation.

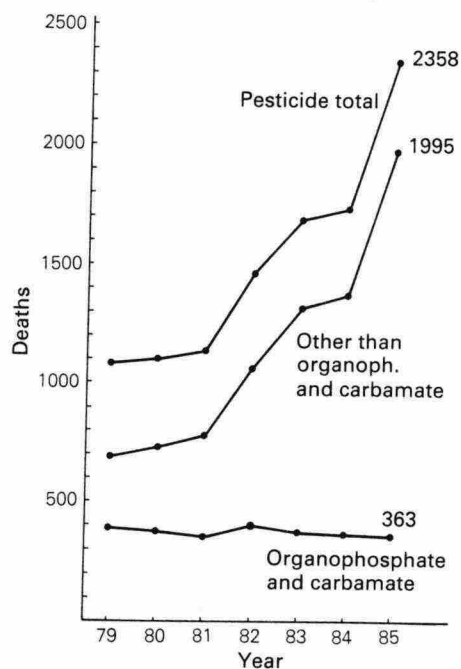


Figure 1 Number of deaths due to pesticide poisoning in Japan

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The absorbance of samples was measured at 603 nm by Hitachi spectrophotometer Model 200-20 and the elution rate of paraquat dichloride was calculated using the following formula:

$$\text{Elution rate (\%)} = \frac{\text{Amount of paraquat dichloride in artificial gastric or intestinal juice}}{\text{Amount of paraquat dichloride in paraquat WDG}}$$

Results

The elution rate of paraquat dichloride from gelled paraquat into artificial gastric and intestinal juices is shown in Table 1 and Figure 2.

In the dynamic study, the elution rates reached only around 50% after 1 h. After that the elution rate was slow and finally reached 68.5% in gastric juice and 65.4% in intestinal juice at 24 h. The elution in the stationary study was slow compared with the dynamic study. This indicates that gelled paraquat, even if ingested, is much safer than liquid formulations. Paraquat WDG can easily be changed to an aqueous solution by diluting the composition with a

Table 1 Elution rate of paraquat dichloride into artificial gastric and intestinal juices

| Time | Elution rate (%) | | | |
|--------|------------------|------------------|---------------|------------------|
| | Stationary study | | Dynamic study | |
| | Gastric juice | Intestinal juice | Gastric juice | Intestinal juice |
| 0 | 1.4 | 5.4 | 7.1 | 6.7 |
| 10 min | 2.6 | 10.2 | 21.4 | 19.4 |
| 30 min | 5.5 | 20.7 | 33.6 | 33.5 |
| 1 h | 9.5 | 23.1 | 41.6 | 38.7 |
| 3 h | 23.7 | 31.5 | 46.9 | 47.3 |
| 6 h | 37.7 | 47.9 | 52.7 | 53.8 |
| 24 h | 48.8 | 60.3 | 68.5 | 65.4 |

large amount of water. The solution has low viscosity, is suitable for spraying, and shows the same efficacy as liquid paraquat on weeds.

Conclusion

This is an important development. If further research can substantiate these observations and prove that the formulation is effective in its intended use, the WDG formulation could well result in a reduction in the number of fatal paraquat intoxications.

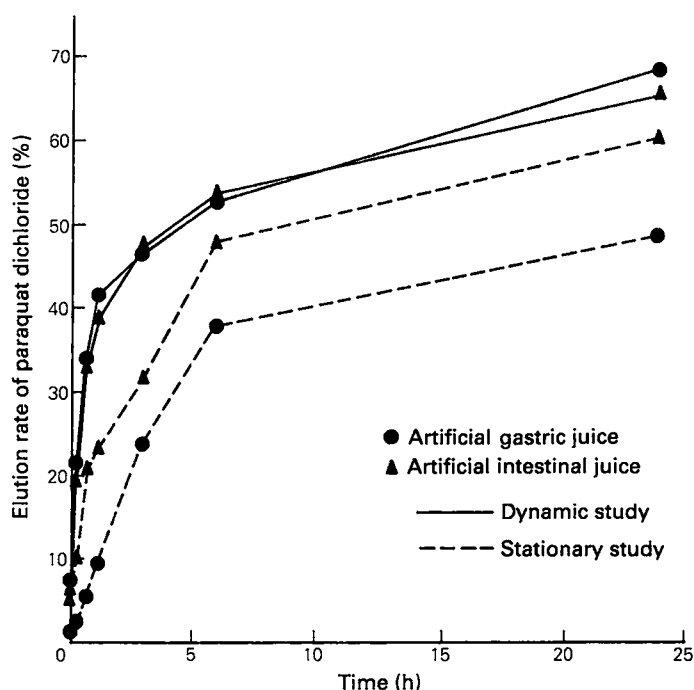


Figure 2 Elution rate of paraquat dichloride into artificial gastric and intestinal juices

The Epidemiology and Prevention of Paraquat Poisoning

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- 1 In the UK there was an increase in the annual number of deaths associated with paraquat poisoning between 1966 and 1975. Since that time there has been little change in numbers.
- 2 High mortality is associated commonly with suicidal intent. Serious accidental poisoning from paraquat has never been frequent in the UK and there have been no deaths reported in children since 1977.
- 3 The National Poisons Information Service has monitored in detail all reports of paraquat poisoning since 1980. Of the 1074 cases recorded there were 209 deaths. In recent years serious poisoning has been more commonly associated with ingestion of concentrated products by males. Local exposure to paraquat has not resulted in systemic poisoning.
- 4 International data for paraquat poisoning is incomplete and difficult to compare. There is a scarcity of morbidity data at both international and national levels. Information obtained from Poison Control Centres indicates that paraquat poisoning occurs in many countries but detailed comparisons are hindered by lack of standardised methods of recording.
- 5 Various measures to prevent paraquat poisoning have been introduced. Their effectiveness has not been studied in detail. Some support is provided by the low incidence of serious accidental paraquat poisoning in the UK, but because of the suicidal nature of paraquat poisoning it is unlikely that current preventative measures will influence the number of deaths occurring each year.
- 6 Preventative measures against paraquat poisoning should be tailored to national needs, based on and assessed by epidemiological studies.

Introduction

The preceding papers have stressed both the importance of paraquat to agriculture, and its safety when correctly used. Paraquat is, nevertheless, toxic to man and this toxicity has been the subject of a great deal of attention in the scientific and 'lay' press. The first cases of paraquat poisoning occurred in 1964, in Ireland and New Zealand (Bullivant, 1966) and by 1970 some 600 fatalities had been reported in the world literature (IPCS, 1984). In spite of the interest, it remains a difficult task to describe the mortality and morbidity associated with paraquat poisoning in different countries in strict epidemiological terms. Such a description requires appropriate and comparable mortality and morbidity statistics. A recent review found that 'because of the different requirements or practices for notification or reporting of cases of poisoning in the many countries in which paraquat is used, the magnitude of the problem is difficult, if not impossible, to determine' (IPCS, 1984). We concur with this view after reviewing the information available from Poison Control Centres, routine sources of mortality and morbidity data and from scientific reports. The information available

from these sources is presented and the measures aimed at preventing paraquat poisoning reviewed.

Sources of information

1. Hospital based surveys

The Home Accident Surveillance Scheme (HASS) records standardised data from a sample of twenty Accident and Emergency (A&E) departments in England and Wales on all types of home accidents (Consumer Safety Unit). A request was made for the number of admissions due to home accidents with weedkillers occurring during the period October 1982 to October 1984. In addition the results of an epidemiological study of acute poisoning cases attending twenty one A&E departments in England and Wales were examined (Murray, Francis & Thompson 1986).

2. Poison Control Centre reports

These reports include the results of a five-year surveillance of paraquat poisoning undertaken by the National Poisons Information Service (NPIS) and the

manufacturer (ICI plc) since 1980. Details of the methods used have been previously published (Hart & Bramley, 1983; Whitehead, Volans & Hart, 1984). In addition the results of a survey amongst European Poison Control Centres of the incidence of paraquat poisoning, undertaken by the secretary of the European Association of Poison Control Centres (EAPCC) (Wickström, 1984) have been examined together with other information from Poison Control Centres given directly to the authors.

3. Mortality statistics

Statistics for England and Wales published in the *Pharmaceutical Journal* for 1966–1973 and by the Office of Population Censuses and Surveys (OPCS) for 1974–1984 have been used. Data was not published in 1981 in England and Wales due to industrial action.

For Scotland, statistics were obtained from the Annual Report of the Registrar General from 1967 to 1984.

4. Other sources

Information from the Agrochemical Poisoning Appraisal Panel (APAP) which is administered by the Health and Safety Executive to investigate reports of occupationally related pesticide poisonings together with information published in the scientific press has been analysed.

Morbidity from paraquat poisoning

1. Hospital based surveys

From October 1982 to October 1984, over 287,000 home accidents were reported to HASS. Of the 39 which were due to weedkillers only seven could be identified as containing paraquat. Four of these involved children under 2 years of age, but only one was admitted into hospital. Limitations in the HASS reporting system, for example fatalities not being included and trade names not always being recorded, may mean that this number of cases is an underestimate.

A preliminary report showed that over a period of one year 22 195 cases of acute poisoning attended A&E departments in England and Wales. Only 14 cases of exposure to paraquat were recorded (Murray *et al.*, 1986). The number of admissions to the hospitals in the study represent approximately 12.5% of all admissions in England and Wales. The total number of exposures due to paraquat may therefore be estimated at 112 but final figures are expected to be higher (J. Francis, personal communication).

A retrospective study of cases of self-poisoning presenting at the United Norwich Hospitals during the

five-year period 1978–1982 found twelve admissions due to paraquat (Adams, 1986).

An important source of morbidity data, the Hospital-In-Patient enquiry (HIPE), fails to document admissions due to paraquat. This is because the International Classification of Diseases (ICD) used for coding the cause of admission has no specific code for paraquat. Any information would be contained in a general category, such as admission due to toxic effects of 'other substances chiefly non-medicinal as to source'.

Outside the UK we found no published national morbidity information concerning paraquat. A national study conducted by the Environmental Protection Agency in the United States concerning hospitalised pesticide poisonings failed to document any cases due to paraquat, even though 2954 admissions due to pesticides were reported in 1974 (G.R.A. and I., 1981).

We therefore concur with a recent report that there are no published national morbidity statistics for pesticides (Vale & Buckley 1986) and that this is particularly true for paraquat. For this reason Poison Control Centres have been identified as potential sources of 'morbidity data' (Brzezinski 1976; Volans & Wiseman, 1986).

2. Poison Control Centre (PCC) reports

(a) *United Kingdom – National Poisons Information Service (NPIS)*. Over the period 1980 to 1985, more than 1000 cases of exposure to paraquat were reported to the NPIS (Table 1). 70% (760) of all cases involved ingestion. Other reported routes of exposure were inhalation (9.8%), skin contact (9.3%), eye contact (2.3%) and injection (0.7%). Of these routes only ingestion and injection led to symptoms of systemic poisoning, though one case of skin contact resulted in a positive urine test.

Of all the cases of ingestion 13% of patients were under five-years-old, 2% were aged between 5 and 12 years, and 85% were older than 12 years. Outcome of the incident was confirmed in 81% of cases (67% survival) by the attending physician, generally about four to five months after the incident. It was not possible to obtain complete follow-up because of difficulties in tracing patients who were not admitted into hospital.

The proportion of survivors having symptoms was estimated for 1984, when 74% of adults had symptoms whereas in the under 5 age group only one child (8.3%) had.

The Agrochemical Poisoning Appraisal Panel recorded three occupationally related paraquat poisonings in 1982.

Thus paraquat poisoning does not seem to represent a problem: to children, by skin and eye contact, inhalation, and through occupational contact.

Table

Year

1980
1981
1982
1983
1984
1985*
Total

S: Surv
* Prov:

Table 2

Country

UK
England
Scotland
Denmark
France
German
Greece
Eire
Netherla
Czechosl
Norway
Poland
Spain
Sweden
Switzerla
Israel
Australia
Fiji
Japan
USA

* Persons

(b) Other
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Table 1 Paraquat cases notified to the NPIS over the years 1980-1985

| Year | Total number of cases | Number of cases of ingestion | Age and outcome of ingestion cases | | | | | | | | | Number of deaths by ingestion | Total number of deaths |
|-------|--------------------------|---------------------------------|------------------------------------|---|----|------------|---|----|----------|-----|-----|----------------------------------|---------------------------|
| | | | < 5 yrs | | | 5 - 12 yrs | | | > 12 yrs | | | | |
| | | | S | D | NK | S | D | NK | S | D | NK | | |
| 1980 | 152 | 121 | 11 | — | 3 | — | — | 1 | 54 | 37 | 15 | 37 | |
| 1981 | 169 | 127 | 4 | — | 2 | 1 | — | — | 57 | 45 | 18 | 45 | 37 |
| 1982 | 223 | 154 | 16 | — | 5 | — | — | 1 | 78 | 38 | 16 | 38 | 47 |
| 1983 | 198 | 143 | 15 | — | 8 | — | — | 5 | 64 | 33 | 18 | 33 | 41 |
| 1984 | 189 | 132 | 12 | — | 9 | 3 | — | 1 | 58 | 32 | 17 | 32 | 33 |
| 1985* | 143 | 83 | 9 | — | 8 | 1 | — | 1 | 26 | 19 | 19 | 19 | 32 |
| Total | 1074 | 760 | 67 | — | 35 | 5 | — | 9 | 337 | 204 | 103 | 204 | 209 |

S: Survival D: Death NK: Not known

* Provisional figures

Table 2 Cases of paraquat poisoning reported internationally

| Country | Cases (fatalities in brackets) | | | | | Source |
|-----------------|--------------------------------|----------|--------------------|----------|----------|-------------------|
| | 1980 | 1981 | 1982 | 1983 | 1984 | |
| UK | 152 (37) | 169 (47) | 223 (41) | 198 (33) | 189 (32) | NPIS |
| England & Wales | (24) | NK | (31) | (36) | (31) | OPCS |
| Scotland | (6) | (12) | (9) | (5) | (9) | Registrar General |
| Denmark | | | (3 over 3 years) | | | Copenhagen PCC |
| France | 90 | 106 | 83 | NK | NK | Wickström* |
| | | 27 (20) | — | — | — | Frelan 1983 |
| Germany (West) | | | (8 from 1978-1983) | | | Wickström* |
| Greece | 25 | 49 | 65 | 85 | 80 | Athens PCC |
| Eire | NK (13) | NK (4) | 59 (9) | 54 (14) | 53 (7) | Dublin PCC |
| Netherlands | 29 | 39 | 19 | NK | NK | Wickström* |
| Czechoslovakia | | | (2 to 3 per annum) | | | Wickström* |
| Norway | | | (3 over 12 years) | | | Wickström* |
| Poland | 6 (3) | 7 (0) | 12 (10) | NK | NK | Wickström* |
| Spain | NK | NK | 7 | NK | NK | Wickström* |
| Sweden | 1 (0) | 2 (0) | 0 | 0 | 0 | Stockholm PCC |
| Switzerland | 10 (1) | 8 (2) | 8 (1) | 6 (3) | 3 (2) | Zurich PCC |
| Israel | NK | (4) | (2) | (0) | (0) | Haifa PCC |
| Australia | NK | NK | 11 | 8 | 10 | Canberra PCC |
| Fiji | — | — | 49 (30) | 59 (33) | — | Groundar 1984 |
| Japan | | | | | (1300) | Naito 1986 |
| USA | NK | NK | NK | NK | 153 (1) | AAPCC 1984 |

* Personal communication

(b) *Other countries* Cases of paraquat poisoning recorded over the period 1980-1984 are shown in Table 2. This shows that there are differences in the extent of paraquat poisoning with relatively little occurring in Sweden, Norway, Czechoslovakia and West Germany. However the comparability of these figures is not known because of the different methods of recording and following-up cases and nature of the services provided by the different countries. For example poison control centres in the United States accept enquiries from members of the public, unlike centres in the United Kingdom.

Mortality from paraquat poisoning

1. National mortality statistics

Figure 1 shows the number of fatalities recorded per year in England and Wales, Scotland and Eire for the period 1965-1984. In England and Wales, the first fatalities due to paraquat poisoning were recorded in 1966. Over the ten-year period to 1975, fatalities increased from 1 to 43 cases per annum with a rapid increase occurring between 1971 and 1975. Numbers since 1975—although fluctuating—have not changed significantly, 31 were recorded in 1984.

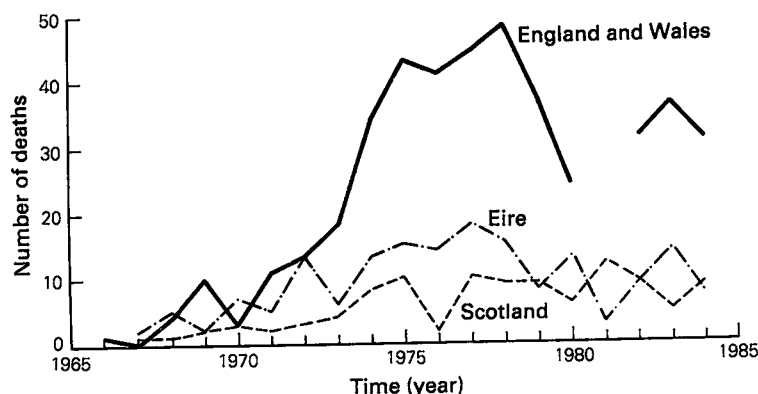


Figure 1 Deaths due to paraquat 1966–1984 for England and Wales, Scotland and Eire
 Sources: England and Wales, *Pharmaceutical Journal* (1966–1973) OPCS DH4 Series (1974–1984).
 Scotland, *Annual Report of the Registrar General* (1966–1984).
 Eire, Fitzgerald *et al.* 1978 (1967–1976). Dublin Poisons Unit (1977–1984).

For Scotland, the trend is similar to that for England and Wales. One case was recorded in 1967 rising to 10 cases in 1975, since when the numbers have remained relatively stable—9 were recorded in 1984.

For Eire, an increase from 1 to 13 fatalities per annum occurred between 1967 and 1972 but since then numbers have been fluctuating at 12 ± 4 per year.

A review of the status of paraquat poisoning in Eire between 1967 and 1976 (Fitzgerald, Barnville, Flanagan *et al.*, 1978) revealed that the mortality in terms of population was approximately seven and a half times that in Great Britain. Figure 2 shows the population-corrected incidence of paraquat poisoning in England and Wales, Scotland and Eire. It can be seen that the incidence of paraquat fatalities in Eire remains high, approximately four times that of England and Wales and twice that of Scotland.

Poisoning with solid and liquid substances in England and Wales remained fairly constant over the period 1973–1980 (Osselson, Blackmore, King *et al.*, 1984) but in recent years (1981–1983) a decline has occurred. Similar trends are seen for Scotland. Over these periods the proportion of deaths due to paraquat continued to increase. Thus, in England and Wales, paraquat has accounted for an average of $1.4 \pm 0.2\%$ of all poisonings with solid and liquid substances since 1975. Over the same period in Scotland it has accounted for an average of $2.3 \pm 0.8\%$ with a maximum of 3.78% being recorded in 1984.

There is thus no evidence to suggest that paraquat poisoning is becoming a less important cause of mortality in the UK.

Information on the intent of the poisoning is recorded at the inquest into the death and can either be

'suicidal', 'accidental' or 'not determined' whether suicidal or accidental. Figure 3 shows the total numbers of fatalities classified into these categories over the period 1966–1984 for England, Wales and Scotland. It can be seen that although the numbers recorded for suicidal intent follow very closely those of the total, numbers due to accidents remain below five per annum, with the exceptions of 1975 and 1976 (10 and 6 respectively). The number of not determined cases reached a maximum in 1977 (12 per annum) coincident with a decline in accidental deaths. However, the influence of this category on the number of accidental deaths remains difficult to interpret, and it is more likely that the number of suicidal deaths would be influenced by the 'not determined' category because of religious and other constraints in bringing in a verdict of suicide. It is clear from these figures that the rise in paraquat fatalities which occurred from the late 1960's to the early 1970's was due to an increase in the use of paraquat for suicide.

Of the 428 deaths recorded as due to paraquat, over the period 1966–1984 in England and Wales, 75% were male and 25% female. 77% of the suicidal deaths and 65% of accidental deaths over this period occurred in males. A similar sex distribution is found for the 105 recorded fatalities in Scotland; 74% of the total were male; 78% of suicides and 59% of accidental deaths were male.

Details regarding age of patient are not available from published mortality statistics which give broad age ranges. However, over the period 1968–1977 six paraquat fatalities occurred in British children under the age of ten; these were accidental in nature. For comparison over the same period 49 children (under

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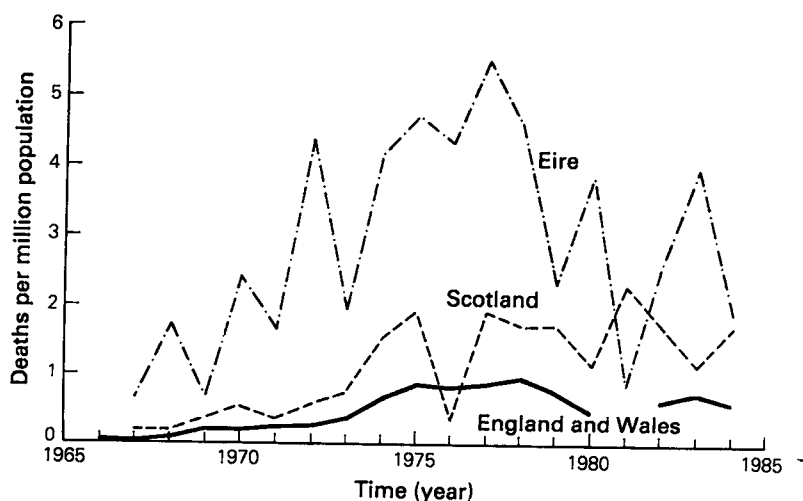


Figure 2 Deaths due to paraquat 1966–1984 per million population for England and Wales and Scotland
Sources: England and Wales, *Pharmaceutical Journal* (1966–1973). OPCS DH4 Series (1974–1984). *Population Trends* 42 1985.
 Scotland, *Annual Report of the Registrar General* (1966–1984). *Population Trends* 42 1985.
 Eire, Fitzgerald *et al.* 1978 (1967–1976). *Report on Vital Statistics CSO Dublin* 1982.

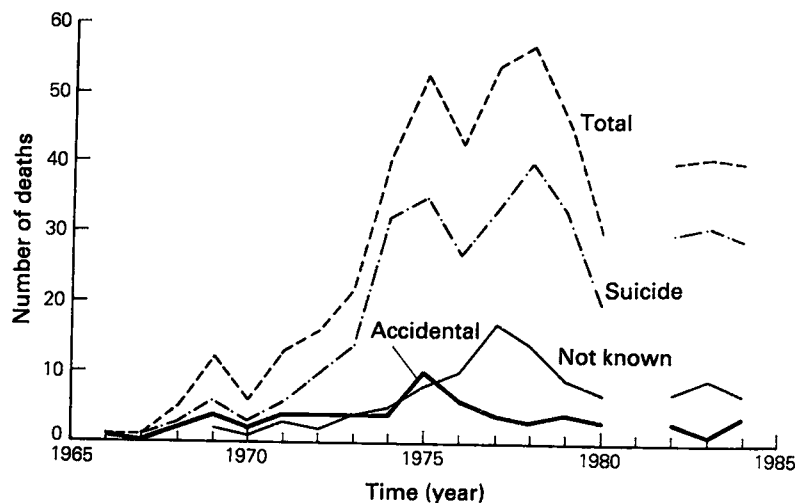


Figure 3 Deaths due to paraquat 1966–1983: Accidents vs suicide, for England, Wales and Scotland
Sources: England and Wales, *Pharmaceutical Journal* (1966–1973). OPCS DH4 Series (1974–1984).
 Scotland, *Annual Report of the Registrar General* (1966–1984).

ten) died as a result of accidental ingestion of tricyclic antidepressants (Frazer, 1980). Since 1977 there have been no reported deaths due to paraquat in this age group.

The Registrar General for Scotland was able to provide details of occupation in 79 of the 81 fatalities occurring from 1975 to 1984. Only in 13 cases (16%)

was there any direct link between occupation and access to paraquat (e.g. farmer, market gardener, groundsman). In Eire it was found that a wide range of occupational types were involved in paraquat poisonings but that intentional poisoning was commonest among agrochemical workers (Fitzgerald *et al.* 1978).

2. Other countries

No national published mortality statistics listing paraquat were found. Data on mortality is published by the World Health Organisation, however only a broad categorisation of poisoning based on ICD codes is given, paraquat therefore is not listed. The same limitations were found with vital statistics available from individual countries.

Additional information regarding fatalities due to paraquat may be obtained from Poison Control Centres.

3. Poison Control Centre reports

a. United Kingdom—National Poisons Information Service. Of the 1074 cases of paraquat exposure reported to the NPIS, 209 cases proved fatal. There was a predominance of males (72%) and of deliberate intent (85%) involved in the fatalities (Table 3). The mean age for males was 44.6 (S.D. = 16.5) and 54.1 for females (S.D. = 14.2).

71% of fatalities involved concentrated liquid formulations (Table 3) and 22% granular formulations. There was a marked predominance of male fatalities involving the liquid formulations (78% male, 22% female) although there was no such difference with the granular products (54% male, 46% female).

Table 3 Type of product, intent and sex of patient involved in 209 fatalities reported to the NPIS (1980–1985)

| | Accidental | Deliberate | NK |
|--------------------|------------|------------|----|
| Liquid concentrate | | | |
| Male | 4 | 100 | 12 |
| Female | — | 30 | 2 |
| Total = 148 | | | |
| Granular | | | |
| Male | 3 | 21 | 1 |
| Female | 2 | 18 | 1 |
| Total = 46 | | | |
| NK | | | |
| Male | — | 8 | 2 |
| Female | 1 | 1 | 3 |
| Total = 15 | | | |
| Totals: 209 | 10 | 178 | 21 |

Note: Liquid concentrate: Gramoxone, Dextrone, Gramonal, Cleensweep
Granular: Weedol, Pathclear

Of the 209 fatalities, 204 were due to ingestion of the product, two were due to injection, one intravenously and one intramuscularly and in three cases the route of exposure was not known.

Information was available as to the geographical distribution of 173 of the fatal cases. In absolute numbers most fatalities occurred in Greater London,

West Midlands and Belfast. However, this could be due to the large populations and/or the presence of centres taking an interest in the treatment of paraquat poisoning. Figure 4 shows that, when corrected for population differences, there are disproportionately large numbers of fatalities (seven or more per million) occurring in Belfast, Devon, Cornwall, Norfolk, West Sussex and West Glamorgan—a pattern which probably reflects the scale of the agricultural industry in these areas.

Information regarding occupation was only available for 67 of the 209 fatalities. Of these 39% had occupations which gave ready access to concentrated paraquat products, the remaining occupations were varied, with no obvious relationship to agriculture.

There are differences between the number of fatalities reported to the NPIS and those recorded from death certificates in England, Wales and Scotland. Both sources of data contain an unknown degree of bias. The NPIS relies principally on voluntary reporting of cases, although since 1980 by following up cases reported to the manufacturer or in newspapers the surveillance has been more complete. Official mortality statistics rely on the correct diagnosis of the cause of death which has been shown to be inaccurate in many instances of poisoning (Vale, Buckley & Meredith, 1984). If the number of deaths reported to the NPIS are compared to those reported by the OPCS and Registrar General of Scotland, the differences are small, e.g. 41 compared with 40 in 1982, 33 compared with 41 in 1983 and 32 compared with 30 in 1984. The degree of overlap remains unknown, requiring comparison of death certificates with NPIS records, and has not been possible within the scope of this study. In Eire, mortality statistics over the period 1967–1976 were obtained from a study combining official mortality and PCC statistics (Fitzgerald *et al.*, 1978), whilst after 1976, statistics were obtained solely from the PCC. There does not seem to be any great jump in the mortality trend shown in Figure 1 so perhaps differences between PCC and official mortality statistics are in fact small.

b. Other countries Mortality data from a survey into the incidence of paraquat poisoning amongst members of the EAPCC is shown in Table 4 together with information from other PCC's and literature. There are wide differences from country to country in the annual numbers of deaths due to paraquat per year, ranging from 1300 in Japan to 1 in Denmark and zero in Sweden. There are also wide variations in the number of fatalities per million population, e.g. 0.004 per million (USA) and 47.0 per million (Fiji). The mortality ratios range from 74% in one French study (Frelon *et al.*, 1983), 58% (Fiji) and 52% (Poland) to 0.6% (USA) suggesting that the proportion of suicides and accidental exposures are different in

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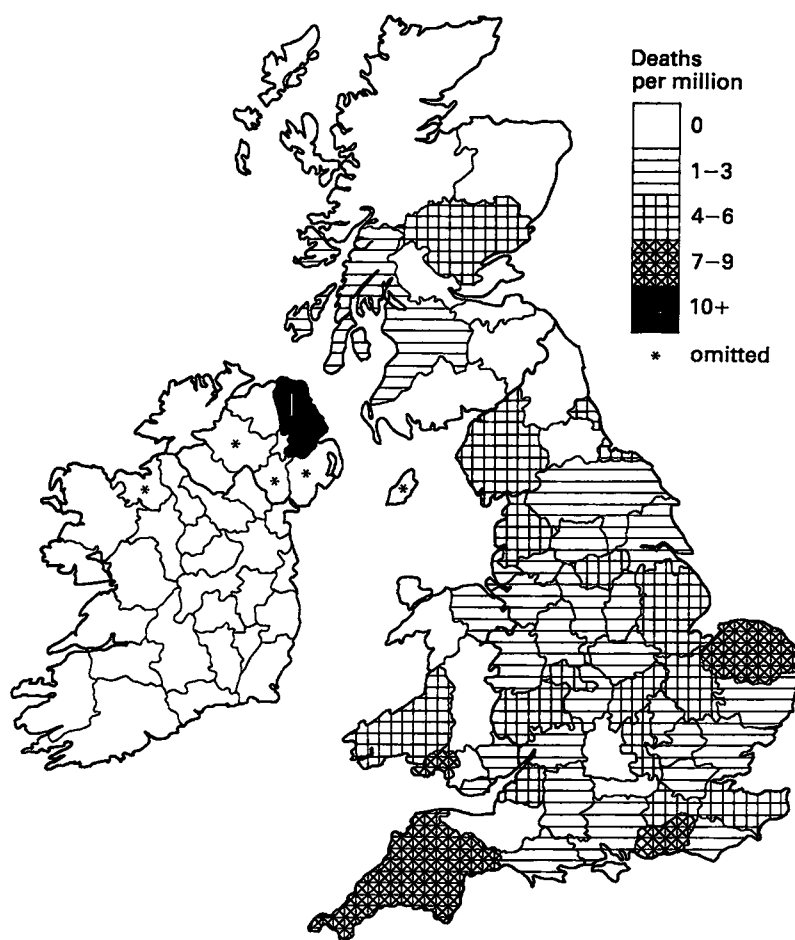


Figure 4 Deaths due to paraquat 1980-1985 (UK): Deaths per million population by county as reported to NPIS. ($n = 173$.)

different countries. Although the figures are not strictly compatible due to uncertainties with the populations covered, they do indicate that some countries have bigger problems with paraquat poisoning than others.

In France, paraquat poisoning has been monitored in detail by Poison Control Centres (Conso, 1979; Frelon, Merigot, Garnier *et al.*, 1983; Ethymiou, 1983). Paraquat was first marketed there in 1965, but fatalities were not recorded until 1973, rather later than in the UK. Accidental deaths declined in proportion to suicides over the period 1973 to 1977. All deaths resulted from ingestion. Ethymiou (1983) reported that although accidental and occupational poisoning represented 74% of all cases, suicidal poisoning was associated with the highest mortality, as were the more concentrated products. Over a

three-year period only one child died. More cases were reported in rural areas. Hence the situation in France is very similar to the UK.

A series of reviews concerning poisoning cases in Malaysia (Amarasingham & Lee, 1969; Amarasingham & Hee, 1976 and Amarasingham & See unpublished data) found that paraquat has replaced arsenite as the most commonly consumed poison. From 1977 to 1981 paraquat was responsible for 31% of all poisoning cases, with 79% mortality. The incidence of males and females was similar and poisoning was predominantly due to its suicidal use by the poorer ethnic groups who presumably had greater access to the product. Accidental cases of poisoning occurred after the concentrated formulations were decanted locally into poorly labelled containers.

Table 4 Fatalities due to paraquat reported internationally (over the years 1980–1984)

| Country | Population (millions) | Deaths per annum (average) | Deaths per million population per annum | Cases per million population per annum | Mortality % (average) | Source |
|-----------------|--------------------------|----------------------------------|--|---|-----------------------------|-------------------|
| UK | 56.6 | 37.6 | 0.66 | 3.3 | 20 | NPIS |
| England & Wales | 49.6 | 30.3 | 0.61 | — | — | OPCS |
| Scotland | 5.2 | 8.2 | 1.6 | — | — | Registrar General |
| Denmark | 5.1 | 1.0 | 0.20 | — | — | Copenhagen PCC |
| France | 54.2 | — | — | 1.7 | — | Wickstrøm* |
| | | 20.0 | (0.36) | (0.5) | 74 | Frelan 1983 |
| Germany (West) | 61.6 | 1.3 | 0.02 | — | — | Wickstrøm* |
| Greece | 9.8 | — | — | 6.2 | — | Athens |
| Eire | 3.5 | 9.4 | 2.7 | 15.8 | 18 | Dublin PCC |
| Netherlands | 14.3 | — | — | 2.0 | — | Wickstrøm* |
| Czechoslovakia | 15.4 | 2.5 | 0.16 | — | — | Wickstrøm* |
| Norway | 4.1 | 0.25 | 0.06 | — | — | Wickstrøm* |
| Poland | 36.7 | 4.3 | 0.12 | 0.23 | 52 | Wickstrøm* |
| Spain | 37.9 | — | — | 0.9 | — | Wickstrøm* |
| Sweden | 8.3 | — | — | 0.07 | — | Stockholm PCC |
| Switzerland | 6.5 | 1.8 | 0.28 | 1.3 | 21 | Wickstrøm* |
| Israel | 4.1 | 1.5 | 0.37 | — | — | Haifa PCC |
| Australia | 15.4 | — | — | 0.6 | — | Canberra PCC |
| Fiji | 0.67 | 31.5 | 47.0 | 80.6 | 58 | Groundar 1984 |
| Japan | 118.4 | 1300 | 11.0 | — | — | Naito 1986 |
| USA | 232.0 | 1.0 | 0.004 | 0.7 | 0.6 | AAPCC |

* = Wickstrøm, E. personal communication

Population sources: Eurostat 'Basic Statistics of the Community' 1984
UK CSO 'Regional Trends' 1985

Prevention

A range of measures have been introduced or proposed for the prevention of paraquat poisoning.

1. Communication

Information concerning the toxicity of paraquat, correct usage and the dangers of inappropriate storage should be given to agricultural and domestic users. Product labelling is one way of communicating this information. The earliest product labels for paraquat gave no indication of its toxicity, but when the problem of poisoning became apparent appropriate changes were made and present day labels leave the user in no doubt about the need to handle the product with care. Labelling should be in an appropriate language with symbols carefully chosen to be meaningful to the user. For example in some parts of the world the snake is more meaningful as a hazard warning of poison than the skull and crossbones.

No matter how good the label, it cannot be assumed that the user will read it carefully. It is therefore important to use additional forms of communication; posters and booklets such as those produced by

GIFAP (GIFAP 1983), appropriate audio visual aids and educational campaigns by the press and television regarding safe handling and storage. Media coverage of paraquat poisoning can have a detrimental effect; reports of individual cases, often sensationalised, may influence others to use paraquat as a means of suicide (Barraclough, Shephard & Jennings, 1977). Therefore restricting or controlling such publicity might help reduce the number of suicides using paraquat (Hayes, 1980).

2. Packaging

Restricting pack size is an obvious way to limit the dose likely to be ingested. Additionally the type of package can affect the accessibility of the product. The proposed Child Resistant Packaging Regulations will not require child resistant closures for paraquat containing products currently on sale in the UK since they will not apply to solids or products exclusively for use in agriculture [Child Resistant Packaging Regulations 1986 (Draft)]. It is unlikely that they would affect the incidence of serious poisoning in children since children do not ingest toxic amounts of

the domestic products or gain access to the commercial preparations in their original containers. Accidental poisoning with these products in adults and children normally occurs as a result of inappropriate decanting and labelling. Packaging changes are unlikely to deter the suicidal patient.

3. Formulation changes

Changes in the concentration of paraquat within a product will also limit the dose ingested. Thus the marketing of a 2.5% w/w granular formulation represents a reduction in hazard from the earlier 5% w/w formulation. It has been shown that the granular formulation is less of a hazard than the liquid concentration (Table 3) and it has been proposed in this respect that a diluted liquid concentrate, 10% w/v, should replace the 20% w/v product currently marketed.

Other formulation changes have involved the use of 'additives'. An unpleasant smelling 'stenching' agent was added to liquid formulations in 1975 and in 1981 a blue colour was added to liquid and solid paraquat products to serve as a warning.

In 1977 a centrally-acting emetic agent, codenamed PP796, was added to liquid formulations at a concentration of 0.05% w/v and to solid formulations at a concentration of 0.02% w/w. This concentration of emetic was calculated to cause vomiting if the minimum lethal dose was swallowed and in animal experiments such a concentration increased the lethal dose of paraquat by a factor of three to five (Rose, 1976). Recently (1985) the concentration of emetic in solid formulations has been doubled. Two authors have commented on the effectiveness of the emetic in reducing mortality in man. In France it was concluded that the emetic (identified in 14 cases, 11 of whom died) did not modify prognosis. In contrast preliminary findings of a study in the UK have found that there may be some reduction in mortality with emetic addition (A. P. Whitehead, personal communication). Emetic addition was not associated with any adverse effects (Denduyts-Whitehead, Hart & Volans, 1985). Even so the efficacy of the emetic at reducing mortality in man remains to be substantiated.

Another suggestion for prevention has been put forward as a result of the development of a novel formulation which forms a semi-solid mixture when small amounts of water are added, thus making it difficult to ingest large quantities (Naito & Yamashita, 1986).

4. Legislation

Legislation has restricted the availability of the commercial concentrate in many countries and in some countries a total ban has been applied (West Germany and Sweden). In the UK the Poisons Act of 1972 restricts the sale of concentrated formulations to

'persons engaged in the trade or business of agriculture, horticulture or forestry'. The sale of these concentrated products is further restricted by limiting the number of licenced dealers. In Eire, similar legislation was passed in 1968 and 1975. The effects of this legislation on the incidence of paraquat poisoning were studied by Fitzgerald *et al.* (1978) who found that there was a drop in the number of accidental poisonings, due to a decrease in the practice of decanting commercial products into household containers. There was no change in the number of suicides after this legislation was passed. Legislation may have the effect of increasing other forms of suicidal poisoning. It was following a ban of arsenite as a weedkiller in Malaysia in 1976 that paraquat poisoning became such a problem (Amarasingham & See, unpublished data). Those countries where paraquat is banned can be seen from Table 2 to have a very low incidence of paraquat poisoning. However such a severe course of action may not be appropriate for all countries and must take into account the agricultural importance of paraquat in that country.

Asked whether measures taken against paraquat poisoning had been effective, members of the European Association of Poison Control Centres (EAPCC) concluded that the addition of an emetic or staining agent had not had the desired effect and that strict regulations on the sale of the liquid concentrate did not seem to be wholly effective (Wickström, personal communication).

Discussion

Comparisons of the incidence and severity of paraquat poisoning between different countries are severely limited by the lack of standardised methods of official data collection and recording. Nevertheless it is apparent that paraquat remains an important cause of mortality worldwide and there is little evidence that paraquat poisoning is decreasing in frequency.

There are differences in the incidence of paraquat poisoning amongst the countries studied. There are also regional differences within the UK, Northern Ireland and Scotland have higher incidences than England and Wales, and paraquat poisoning in Eire has always had a higher incidence than in the UK. In some countries paraquat has not so far presented a serious problem in spite of its widespread usage—for example, USA and Australia. In contrast Japan and a number of other countries, notably Fiji, are currently facing epidemics of paraquat poisoning far more severe than those seen in Europe.

Mortality from paraquat poisoning is closely related to suicidal intent; thus in the USA (mortality 0.6%) 88% of cases were accidental whilst in Fiji (mortality 58%), 66% had suicidal intent. Additionally the predominance of males amongst fatalities correlates well

with the known epidemiology of suicides (Weissman, 1974).

The increase in suicidal use of paraquat in the UK over the period 1966–1975, accounts for the rise in fatalities (Figure 3). Why there should have been this increase in so many countries is unknown. In the UK there was no proportionate increase in sales of the commercial product over the period when the rapid increase in fatalities occurred (T. B. Hart, personal communication). However the availability of the liquid concentrate remains an important factor. The wide range of occupations recorded amongst fatalities may mean that legislation restricting the availability of paraquat is not sufficient. Substitution and public awareness are additional factors which may influence the use of a particular product for suicide (Low *et al.*, 1981). Substitution has been shown to have had an effect in Malaysia where paraquat replaced arsenite poisoning but the influence of substitution in the UK is not known. Public awareness, increased by media reporting may be an important factor but remains difficult to investigate.

In many countries serious accidental and occupational poisoning and poisoning in children is rare. The nature of paraquat poisoning is largely suicidal and it is unlikely that current preventative measures

will influence the number of deaths occurring each year. Few preventative measures have been monitored in such a way as to demonstrate their effectiveness.

On the basis of our experience in the UK, we believe that Poison Control Centres (PCCs) have an important role in monitoring the incidence and severity of poisoning and providing epidemiological data. PCCs are well placed then to develop schemes to evaluate preventative measures. Care must be taken when making direct comparisons between different PCCs because of the different populations covered and differences in the methods used to assess cases. There is currently much interest in the suggestion that PCCs should agree to standardise some aspects of data collection. We would tentatively suggest that since paraquat poisoning in Europe is widespread and involves relatively small numbers of a discrete type of poisoning it would form a useful model for international collaboration between PCCs.

The authors acknowledge the help of colleagues in the National Poisons Information Service and other Poison Control Centres and, in particular, the information provided by Dr E. Wickström and Professor A. N. J. van Heijst on behalf of the European Association of Poison Control Centres. We should also like to thank John Gelder for his help with the illustrations.

References

- ADAMS, R. H. M. (1986). An accident and emergency department's view of self-poisoning. A retrospective study from the United Norwich Hospitals: 1978–1982. *Human Toxicol.*, **5**, 5–10.
- AMARASINGHAM, R. D. & LEE, H. (1969). A review of poisoning cases examined by the Department of Chemistry, Malaysia, from 1963 to 1967. *Med. J. Malaysia*, **XXIII** (3), 220–227.
- AMARASINGHAM, R. D. & HEE, T. T. (1976). A review of poisoning cases examined by the Department of Chemistry, Malaysia, from 1968 to 1972. *Med. J. Malaysia*, **XXX** (3), 185–193.
- AMARASINGHAM, R. D. & SEE, L. A. (unpublished report). A review of human poisoning cases examined by the Toxicology Division of the Department of Chemistry, Petaling Jaya, Malaysia, from 1977–1981.
- BARRACLOUGH, B., SHEPHERD, D. & JENNINGS, C. (1977). Do newspaper reports of Coroners' inquests incite people to commit suicide? *Br. J. Psych.*, **131**, 528–532.
- BRZEZINSKI, Z. J. (1977). Poisoning in the European Region. *Acta Pharmacol. Toxicol.*, **41** (Suppl 2), 470–484.
- BULLIVANT, C. M. (1966). Accidental poisoning by paraquat. Report of 2 cases in man. *Br. Med. J.*, **1**, 1272–1273.
- CHILD-RESISTANT PACKAGING (Safety Regulations) 1986 (Draft). Department of Trade and Industry, United Kingdom.
- CONSO, F. (1979). Paraquat poisoning: experience of Poison Control Centers in France. *Vet. Hum. Toxicol.*, **21** Suppl, 112–113.
- Consumer Safety Unit. The Home Accident Surveillance System (H.A.S.S.). Published annually. Department of Trade and Industry. United Kingdom.
- DENDUYT-WHITEHEAD, A. P., HART, T. B. & VOLANS, G. N. (1985). Effects of the addition of an emetic to paraquat formulations on acute poisoning in man. *J. Toxicol. Clin. Tox.*, **23**, 422–423.
- EFTHYMIU, M.-L. (1983). Resultats d'une enquete nationale sur trois ans concernant les intoxications par paraquat. *Xeme. Symposium national de medicine Agricole*, 29 April 1983.
- FITZGERALD, G. R., BARNVILLE, G., FLANAGAN, M. *et al.* (1978). The changing pattern of paraquat poisoning: An epidemiologic study. *J. Irish Med. Assoc.*, **71** (4), 103–108.
- FRAZER, N. C. (1980). Accidental poisoning deaths in British children 1958–1977. *Br. Med. J.*, **280**, 1595–1598.
- FRELON, J. H., MERIGOT, P., GARNIER, R., BISMUTH, C. & EFTHYMIU, M.-L. (1983). Facteurs pronostiques de l'intoxication aigue par le paraquat etude retrospective sur les cas enregistries au Centre Anti-Poisons de Paris en 1981. *Toxicol. Eur. Res.*, **5** (4), 163–169.
- GIFAP (Groupement International des Associations Nationales de Fabricants de Produits agrochimiques) (1983). Guidelines for the safe and effective use of pesticides. Published by GIFAP, Brussels.
- GOVERNMENT REPORTS, ANNOUNCEMENTS AND INDEX (1981). National Study of Hospitalised Pesticide Poisonings. U.S.A.
- GROUNDAR, R. P. (1984). Paraquat poisoning in Fiji (Abstract). *J. Forensic. Sci. Soc.*, **24** (4), 376.

- HART, T. B. & BRAMLEY, A. (1983). Paraquat Poisoning in the United Kingdom (Abstract). *Human Toxicol.*, 2, 417.
- HAYES, W. J. (1980). Factors limiting injury from pesticides. *J. Environ. Sci. Health*, B15 (6), 1005-1021.
- IPCS (International Programme on Chemical Safety) (1984). Environmental Health Criteria 39. Paraquat and Diquat. p. 74.
- LOW, A. A., FARMER, R. D., JONES, D. R. & RHODE, J. R. (1981). Suicide in England and Wales: an analysis of 100 years 1876-1975. *Psychol. Med.*, 11, 359-368.
- MURRAY, V. S. G., FRANCIS, J. & THOMPSON, N. (1986). The incidence of paraquat poisoning in an epidemiological study (Abstract). *Human Toxicol.* (this issue).
- NAITO, H. & YAMASHITA, M. (1986). Present status of paraquat poisoning in Japan and a new safe formulation of paraquat (Abstract). *Human Toxicol.* (this issue).
- Office of Population Censuses and Surveys (1975). DH4 Series. Mortality - accidents and violence. Table 10.
- OSSELTON, M. D., BLACKMORE, R. C., KING, L. A. & MOFFAT, A. C. (1984). Poisoning-associated deaths for England and Wales between 1973 and 1980. *Human Toxicol.*, 3, 201-221.
- ROSE, M. S. (1976). The concentration of PP796 required to produce emesis in experimental animals and an estimation of the emetic dose in man. ICI plc, Central Toxicology Laboratory Report No. CTL/R/390/R and 391.
- VALE, J. A. & BUCKLEY, B. M. (1986). Intoxication by pesticides. In *Proceedings of the Conference on the Prevention of Accidental Poisoning in Childhood*, Brussels. 21-22 Nov. 1985, ed. W. Rogmans. European Consumer Safety Association: Amsterdam.
- VALE, J. A., BUCKLEY, B. M. & MEREDITH, T. J. (1984). Deaths from paracetamol and dextropropoxyphene (distalgesic) poisoning in England and Wales in 1979. *Human Toxicol.*, 3, 1355-1435.
- VOLANS, G. N. & WISEMAN, H. M. (1986). Epidemiology of accidental poisoning of children in the European Region. In *Proceedings of the Conference on the Prevention of Accidental Poisoning in Childhood*, Brussels. 21-22 Nov. 1985, ed. W. Rogmans. European Consumer Safety Association: Amsterdam.
- WEISSMAN, M. A. (1974). The epidemiology of suicide attempts 1960-1971. *Archs Gen. Psychiatry*, 30, 737-746.
- WICKSTRØM, E. (1984). The frequency and problems of paraquat poisoning in Europe, as experienced by the Poison Control Centres. (Abstract) Presented at the Xth International Congress of the European Association of Poison Control Centres, Stockholm. 17-20 June 1986.
- WHITEHEAD, A. P., VOLANS, G. N. & HART, T. B. (1984). Toxicovigilance for pesticides. Paraquat poisoning in the United Kingdom. *J. Toxicol. Medicale*, 1, 5-53.

CARDIO-RESPIRATORY EFFECTS OF PARAQUAT WITH AND WITHOUT EMETICS ON WISTER RATS*

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ABSTRACT. We investigated the effects of paraquat products both containing and devoid of emetics on the cardio-respiratory functions of Wister rats. Anesthetized rats were administered intravenously 0.46 ml/kg Gramoxone, a commercial product containing 24% paraquat and an emetic. Paraquat equivalence equalled 110 mg/kg body weight. ECG and respiratory curves were recorded with a polygraph. Fifteen seconds after injection, A-V block and bradycardia occurred and the heart stopped beating soon after. Though the heart was severely affected, the respiratory curve differed very little from pre-injection values. Administration of pure, 24% paraquat solution (110 mg/kg body weight) inhibited respiration and almost no change was recorded by the ECG. Administration of Paragreen A, a commercial product containing 24% paraquat with no emetic, produced slight change in the ECG but respiration soon became strained and stopped. In accordance with this data, we propose that the emetic contained in Gramoxone is primarily responsible for the cardiovascular failure.

Paraquat is a herbicide widely used in Japan since 1965. Poisonings caused by accidental and suicidal ingestion have been increasing yearly. It is known that the toxic effects caused by paraquat consumption are fibrosis of the lung in chronic cases (1) and total dysfunction of the liver (2) and kidney in acute cases. Myocarditis and adrenal cortical necrosis have also been reported as toxic effects of paraquat (3, 4). Most of the investigations attempting to explain the mechanisms that render paraquat toxic focus on the relationship between the paraquat induced superoxide generated in the body and the toxic changes in the tissues (5). However, when we investigate paraquat poisonings, we must note that paraquat is sold as a mixed product. The commercial mixed products in use contain 24% paraquat dichloride (or paraquat sulfate) and additives. For example, Gramoxone, the commercial product most widely used in Japan contains an emetic, in addition to 24% paraquat dichloride, a surface active agent and artificial coloring.

We investigated the effects induced by mixed commercial products containing paraquat on cardio-respiratory functions. We reported here that the additives in particular cause severe damage in an acute period of time.

MATERIAL AND METHODS

Male Wister rats weighing 250-350 g were used for the investigation of drug-induced changes in physiological functions. Respiratory curves and electrocardiographs were recorded by Polygraph system (Nihon Kohden Co Ltd). Rats were anesthetized with sodium pentobarbital (9 mg/kg, ip) and stabilized after 60 minutes.

Drugs administered to the anesthetized, stabilized rats via a catheter inserted into the left femoral vein were: Gramoxone, a

commercial product containing 24% paraquat dichloride, an emetic, a surface active agent, artificial coloring; pure paraquat dichloride; and Paragreen A, commercial product containing 24% paraquat dichloride, a surface active agent and artificial coloring but no emetic. Pure paraquat dichloride was used as a 24% solution with saline. Volumes of iv injected drugs (paraquat equivalence) were: Gramoxone, 0.46 ml/kg body weight (110 mg/kg); 24% pure paraquat solution, 0.46 ml/kg (110 mg/kg) or 1.29 ml/kg (310 mg/kg); and Paragreen A, 0.46 ml/kg (110 mg/kg). Each test group contained 4 or more rats.

A canule equipped with a thermo-sensor (TR-602T Nihon Kohden Co Ltd) was inserted into the trachea to monitor respiration. The following index was used to estimate respiration: R_i = amplitude of respiratory curve / inspiratory time of respiratory curve. ECG was recorded by application to the left front foot, right front foot, and right rear foot.

RESULTS AND DISCUSSION

Administration of Gramoxone

Approximately 10 sec after injection of Gramoxone (0.46 ml/kg; paraquat equivalence = 110 mg/kg body weight), bradycardia was observed. Thereafter prolongation of the QRS time and the P-Q interval occurred. A switch over to the A-V block was noted. Disappearance of the P-wave and excessively prolonged QRS time occurred in succession just prior to complete strain of the ECG wave. The aforementioned changes occurred within 20 sec of injection. Subsequent irreversible impediments to the cardiac conduction system, atrial muscles and ventricular muscles occurred, and the heart stopped beating soon after. Though the cardio-vascular system was thus affected, regularity of respiration was maintained and R_i increased approximately 10%. Respiration continued until 30 sec after injection (Figure 1).

Administration of Pure Paraquat

Within 10 sec after administration of pure

*This paper is based on a presentation at the 1985 AACT/AAPCC/ABMT/CAPCC Scientific Meeting, 4-9 August 1985, held in Kansas City, Missouri.

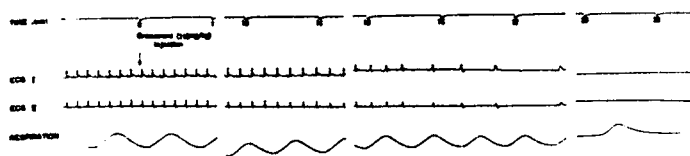


Fig 1. Administration of Gramoxone (110 mg/kg)

24% paraquat solution (0.46 ml/kg; paraquat equivalence = 110 mg/kg), respiration was inhibited up to 15%, with 15-20% continued inhibition occurring thereafter (Figure 2). The ECG for the initial period of 30 sec showed no concurrent change, though slight bradycardia occurred and recovered after this initial period. In one case, however, following slight prolongation of the P-Q interval, a second A-V block (Wencke-Bach type) appeared, but was not sustained for more than 15 sec.

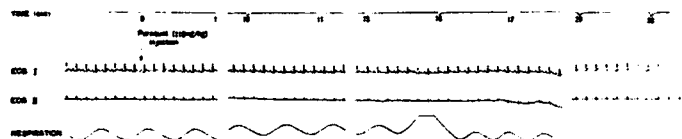


Fig 2. Administration of paraquat (110 mg/kg)

Administration of pure 24% paraquat solution (1.29 ml/kg; 310 mg/kg body weight) inhibited respiration immediately and within 15 sec respiration was inhibited completely. Bradycardia and a slight prolongation of the P-Q interval developed following complete respiratory inhibition. Thirty sec after recorded inhibition, severe bradycardia occurred accompanied by a change in the P-wave or a second degree A-V block. Bradycardia severity progressed gradually for several minutes until the heart stopped beating completely (Figure 3).

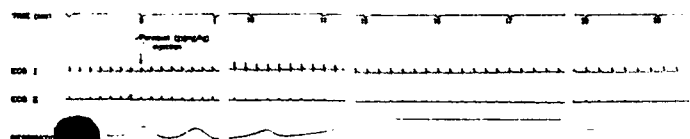


Fig 3. Administration of paraquat (310 mg/kg)

Administration of Paragreen A

Administration of Paragreen A (0.46 ml/kg; paraquat equivalence 110 mg/kg body weight) completely inhibited respiration within 15 sec. During this time the heart rate decreased only gradually and slight prolongation of the QRS time was recorded by the ECG. Approximately 30 sec after injection, slight prolongation of the P-Q interval was observed and some case showed changes in the P-wave after 2 min. These changes recorded by the ECG suggest the existence of impediments to ventricular muscles and the cardiac conduction system (Figure 4).

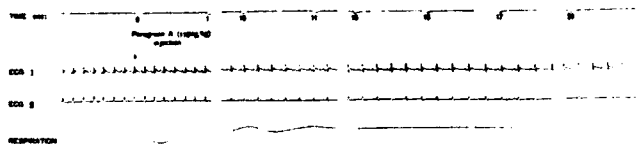


Fig 4. Administration of Paragreen A (110 mg/kg)

These physiological functional changes were almost the same in all rats of each respective test group.

Having studied the data, we note that Gramoxone induced changes in the ECG within 15 sec of administration; thereafter the proper functions of the cardiac conduction system, atrial muscles and ventricular muscles are impeded. Respiratory functions continue somewhat normally throughout this period and even at the time of heart stoppage. Administration of pure paraquat solution or Paragreen A (recall that Paragreen A contains a surface active agent and artificial coloring like Gramoxone, but contains no emetic) had no effect on the heart as severe as the effect of Gramoxone. Since the changes recorded by the ECG in the instances of paraquat or Paragreen A administration were accompanied by respiratory inhibition, we must account for the effect of hypoxia on cardiac functions. Thus we conclude that the emetic contained in Gramoxone was primarily responsible for the decisive cardio-vascular failure. Yet because the transient cardiovascular failure caused by paraquat recovered before respiration recovered, we can not deny the effect of paraquat itself on cardiovascular system.

This study also makes clear the concentration dependent, inhibitory effects on respiration caused by paraquat. But it is not known whether respiratory response to paraquat are regulated by peripheral or central respiratory mechanisms. Paragreen A inhibits respiration most severely, and respiratory inhibition by Paragreen A is similar to that of a large dose of pure paraquat solution. In other words, Paragreen A inhibits respiration about three times more severely than paraquat. The differences of paraquat concentration in tissues between administration of pure paraquat solution and a mixed product are thought to be responsible for the different effects on cardiorespiratory functions. It has been already reported that surface active agents such as sodium taurodeoxycholate and polysorbate 80 facilitate movement of drugs into tissues (6, 7). Therefore, it is supposed that the surface active agent contained in the mixed products augments the effects of paraquat on respiratory function. We further speculate that the emetic contained in Gramoxone facilitates respiration, judging from no inhibition of respiration, although Gramoxone contains a surface active agent like Paragreen A.

CONCLUSIONS

1. Administration of Gramoxone caused irreversible impediments to the cardiac conduc-

tion system, atrial muscles and ventricular muscles. The emetic contained in Gramoxone is primarily responsible for the decisive cardiovascular failure.

2. Paraquat had the concentration dependent, inhibition effects on respiration. A large dose of paraquat inhibited respiration completely.

3. The mild effect of paraquat itself on the cardiovascular failure was suggested.

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REFERENCES

1. Copland GM, Kolin A and Shulman HS: Fatal Pulmonary Intra-Alveolar Fibrosis After Paraquat Ingestion. *N Engl Med* 291:290-292, 1974.
2. Matsumoto T, Matsumori H, Kuwabara N, Fukuda Y and Ariwa R: A Histopathological Study of the Liver

in Paraquat Poisoning. An Analysis of Fourteen Autopsy Cases with Emphasis on Bile Duct Injury. *Acta Pathol Jpn* 30:859-870, 1980.

3. Misawa S, Noguchi N, Nakamura T, Tsuchiya S and Yamamoto H: Pathophysiological Changes of Rabbits in Acute Paraquat Poisoning. *Jpn J Legal Med* 38: 592, 1984.
4. Reif RM and Lewisohn G: Paraquat Myocarditis and Adrenal Cortical Necrosis. *J Forens Sci Soc* 28: 505-509, 1983.
5. Raffin TA, Simon LM, Douglas WH, Theodore J and Robin ED: The Effects of Variable O₂ Tension and of Exogenous Superoxide Dismutase on Type II Pneumocytes Exposed to Paraquat. *Lab Invest* 42: 205-208, 1980.
6. Feldman S and Gibaldi M: Physiologic Surface-Active Agents and Drug Absorption I. Effect of Sodium Taurodeoxycholate on Salicylate Transfer Across the Everted Rat Intestine. *J Pharm Sci* 58: 425-428, 1969.
7. Levy G and Anello JA: Effect of Complex Formation on Drug Absorption V. Studies on the Mechanism of the Secobarbital Absorption-Enhancing Effect of Polysorbate 80 in Goldfish. *J Pharm Sci* 57:101-104, 1968.

USE OF A LINE CARD SEQUENCER FOR TRIAGE OF POISON CENTER CALLS*

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ABSTRACT. In 1984 the Poison Center installed a Dacon ACS-46 Automatic Call Sequencer. This device is connected to all incoming poison information lines (with the exception of a specially designated 911 line) and acts as an interface between callers and Poison Information Specialists during periods of heavy call loads. While the use of a call sequencer could never be termed ideal, such use offers a number of specific benefits in situations that are frequently encountered in Poison Center work. These benefits include: significant reduction in staff stress, caller assurance that a correct number has been reached, efficient triage of incoming calls, and accumulation of accurate incoming call data. Data input parameters of this system include: total calls offered, dropped calls, calls over alarm time, average time for completed calls, average time for dropped calls, and completed and dropped hold time data bins.

In 1984 the Poison Center installed a Dacon ACS-46 Automatic Call Sequencer. This device is connected to all incoming poison information lines (with the exception of a specially designated 911 line) and acts as an interface between callers and Poison Information Specialists during periods of heavy call loads.

The ACS-46 Call Sequencer is capable of processing incoming telephone calls on telephone lines as follows: The ringing of an incoming telephone call is detected by the ACS-46 circuitry. The call is answered by the sequencer after four audible rings (on the caller's end) and a taped message is

then presented to the calling party. The taped message says: "This is the Hennepin Poison Center. Please do not hang-up. All emergency calls are being handled on a priority basis, and a Poison Information Specialist will be with you momentarily. If you feel you have a life-threatening emergency, please call 911." The calling party is then placed on hold and the call is lined up in chronological sequence with any other waiting calls. The lamps on the telephone set flashes at a rate pertaining to the calling sequence: the lamp for the line with the oldest call is fluttered at the "priority rate" of 240 flashes per minute. This rapid fluttering of one lamp indicates to the Poison Information Specialists which line should be answered next. The lamps for the other lines are flashed at a standard rate of 30 impulses per minute. Immediately after the Poison Information Specialist

*This paper is based on a presentation at the 1985 AACT/AAPCC/ABMT/CAPCC Scientific Meeting, 4-9 August 1985, held in Kansas City, Missouri.

SCIENTIFIC REPORTS

Papers published in this section are reviewed by at least two qualified referees for accuracy, scientific soundness, experimental design, data analysis, and interpretation. Papers accepted may result from original research, critical literature reviews or well documented field investigations.

EMETIC EFFECT OF TRIAZOLOPYRIMIDINE, A PYRIMIDINE COMPOUND, IN DOGS

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ABSTRACT: The intention of this study was to determine the minimum required dosage of triazolopyridine (TAP) to consistently induce emesis in canines. We administered single oral doses of TAP to 42 adult beagle dogs. The effect of TAP dosage on emesis was highly significant. The effective emetic dosages were 4.0 mg/10 ml water/animal ($p < 0.05$) and 8.0 mg/10 ml water/animal ($p < 0.01$). In all the dogs tested, 8.0 mg of TAP successfully induced emesis. The mean latency of emesis in the beagle group studied was 15 min, 54 sec (95% confidence limits=8 min, 11 sec to 23 min, 38 sec). Intravenous apomorphine HCL was used to demonstrate the effectiveness of anti-emetic pretreatment with subcutaneous chlorpromazine (CPZ). Pretreatment with CPZ appeared to inhibit apomorphine-induced emesis, but did not modify the emetic response elicited by TAP. Emesis following the administration of TAP was considered a result of direct action of TAP upon the gastrointestinal mucosa. Eighty adult mongrel dogs were also given TAP doses of 4.0 mg/10 ml water/animal, with 100% effectiveness in inducing emesis.

The recent widespread use of agricultural chemical compounds, such as insecticides and herbicides, have resulted in an ever-increasing incidence of poisoning in man, including suicide, homicide and casualties in men and animals due to inadvertent ingestion (1-11). To significantly lessen or to prevent the incidence of death from the ingestion of these necessary but toxic chemical compounds, the addition of an emetic agent to these agricultural chemical compounds has been recommended as a method for minimizing the intracorporeal absorption of these compounds.

The emetic agent or agents to be added to the agricultural compounds should have the following properties: A strong emetic effect at the lowest possible dose; a short latency period prior to emesis; very low intrinsic toxicity; and stability and no lessening of its emetic effect when mixed with agricultural compounds. In the search for an effective emetic agent that satisfies these requirements, Jonouchi et al (12) have reviewed the emetic effects of copper sulfate and tartar emetic. Akahori et al (13) have also re-examined the effectiveness of tetra-potassium pyrophosphate (TKPP), which had been introduced by Weaver et al (14), as an excellent emetic. Despite these efforts, no satisfactory results for emetic agents to be added to agricultural compounds have yet been obtained.

Triazolopyrimidine (TAP), a pyrimidine compound, was reported by Rose (15, 16) to have an emetic effect. In his paper, the emetic effect of TAP and the mechanism of its action were investigated in beagle dogs.

MATERIALS AND METHODS

Experiment I. Determination of the Effective Emetic Dose of TAP in Beagle Dogs

From approximately 60 beagle dogs purchased from a dog breeder in Yamanashi Prefecture, Japan, 58 canines, regardless of sex, and weighing approximately 8.0 kg each were selected. Sixteen animals were used in a preliminary experiment and the remaining 42 were utilized in subsequent studies. The dogs were placed in individual cages, under controlled conditions of 22.0 C (± 2.0 C) and relative humidity of 67% (± 12 %). They were fed a total of 400 g/day, divided into two separate feedings, of commercial solid diet (New Kenz Economy, Sanwa, Kagaku, Nagoya), with water ad libitum.

The emetic agent to be evaluated, TAP, was supplied to us through the courtesy of ICI, Japan (Tokyo). TAP was administered by the method of Akahori et al (13). After an 18-20 hour fasting period, the dogs were given 100 g of the solid diet mixed with 50 ml of meat soup. This meal was consumed thirty minutes prior to the commencement of our experiment. The TAP solution was administered directly into the stomach via a stomach tube. A preliminary experiment was performed to determine the effective emetic dose of TAP needed and the minimum number of samples required.

Preliminary Experiment (Table 1). Sixteen beagle dogs were divided into 4 equal groups. The dosages tested were: Group 1, 0.8 mg/10 ml/animal TAP; Group 2, 2.0 mg/10 ml/animal TAP; Group 3, 4.0 mg/10 ml/animal

Table 1. TAP Dosages for Obtaining Dogs for Study

| TAP dosage (mg/10ml/animal) | Dogs tested | Dogs vomiting |
|--------------------------------|-------------|---------------|
| 0.8 | 4 | 1 |
| 2.0 | 4 | 2 |
| 4.0 | 4 | 4 |
| Water(10ml) | 4 | 0 |

TAP : Triazolopyrimidine

TAP; Group 4 was treated as a control group and was given 10 ml water/animal, which corresponded to the maximum volume used for all the groups. Vomiting occurred in 100% (4 of 4), in Group 3 (4.0 mg TAP) and was not observed (0%) in Group 4, the control group. The tolerable error in comparing both groups (Group 3 and Group 4), assuming the error of emetic incidence to be approximately 45%, was considered not to be overlapping. The number of samples required to meet the above estimation was derived from the nomogram of Takizawa (17) and was determined to be seven per group. The animals were divided into 6 groups, with 7 dogs in each and treated with TAP as follows: 0.5 mg/10 ml/animal; 1.0 mg/10 ml/animal; 2.0 mg/10 ml/animal; 4.0 mg/10 ml/animal; 8.0 mg/10 ml/animal; or as a control group 7 dogs were administered 10 ml of water per animal (Table 2).

Statistical Analysis. To evaluate the emetic effect of TAP, the data obtained in our experiment were examined using the χ^2 Test.

Experiment II. Repetitive TAP Administration

The effects of repeated TAP administration on the frequency and latency of vomiting were investigated using dogs in which emesis had already been induced by TAP. The beagle dogs participating in this study were chosen (4 each) at random from Groups 4 and 5 (Exp 1) whose threshold emetic doses were 4.0 mg/10 ml/animal and 8.0 mg/10 ml/animal, respectively. TAP was administered at intervals of 1 week, over a total period of 7 weeks, using the same administration route as in Experiment 1.

Table 2. Experimental Design for TAP Dosages in Beagle Dogs

| Group | TAP dosage (mg/10ml/animal) | Dogs tested |
|-------|--------------------------------|-------------|
| I | 0.5 | 7 |
| II | 1.0 | 7 |
| III | 2.0 | 7 |
| IV | 4.0 | 7 |
| V | 8.0 | 7 |
| VI | 0 (Water:10ml/animal) | 7 |

TAP : Triazolopyrimidine

Experiment III. The Action Mechanism of TAP

Fifty-five adult, mongrel dogs, both male and female, weighing from 7-14 kg and considered to be conditioned random source dogs (18) were selected from the Animal Protection Center, Kanagawa, Japan. The drugs used in this experiment were obtained from ICI Japan (TAP), Sigma Chemical Co, MO, USA (Apomorphine HCl), and Shionogi Seiyaku, Osaka (Chlorpromazine-CPZ).

Using apomorphine, a central emetic drug as our positive control, the induction of emesis by TAP in CPZ-pretreated animals was studied (Table 3). An 8.0 mg/10 ml/animal dose (1% significance level) was used, as this was the dosage determined to be effective from the results of Experiment 1. From reference to previous experimental literature (19-22), we decided to use a dosage of 200 ug/animal of apomorphine, administered iv. The CPZ dosage was based on the experimental results of Weaver et al (14) set at 20 mg/kg and administered sc. The effects of CPZ pretreatment were evaluated using the X2 Test.

Experiment IV. The Frequency of TAP-Induced Emesis in Mongrel Dogs

The emetic effects of an 8.0 mg/10 ml/animal TAP dose (which was effective in beagle dogs in Experiment I) was confirmed using 80 mongrel dogs (weighing from 7-14 kg). This group of animals consisted of both male and female dogs chosen from 140 mongrel dogs that were obtained from the Animal Protection Center, Kanagawa, Japan, and this group was also considered to be conditioned random source dogs as defined by Yamauchi (18).

Table 3. Effects of CPZ on TAP-Induced Emesis

| Group | Dogs tested | Treatment |
|-------|-------------|---|
| I | 11 | Apomorphine 200 ug/animal (IV) |
| II | 11 | Apomorphine 200 ug/animal (IV) after 30min.CPZ 2.0mg/kg(SC) |
| III | 11 | TAP 8mg/10ml/animal (PO) |
| IV | 11 | TAP 8mg/10ml/animal (PO) after 30min.CPZ 2.0mg/kg(SC) |
| V | 11 | Water 10ml/animal (PO) |

CPZ : Chlorpromazine
TAP : Triazolopyrimidine

RESULTS

Experiment I. Determination of the Effective Emetic Dose of TAP in Beagle Dogs

Table 4 illustrates the effective emetic dose of TAP in beagle dogs, as determined from our experimental results. TAP-induced emesis was observed in 1 dog of the 0.05 mg/10 ml/animal group, in none of the 1.0 mg/10 ml/animal group, in 1 of the 2.0 mg/10 ml/animal group, in 4 of the 4.0 mg/10 ml/animal group, and in all 7 of the 8.0 mg/10 ml/animal group. No emesis was observed in our control group. Our results were

Table 4. Effect of TAP at Various Dosages in Beagle Dogs

| TAP dosage (mg/animal) | Dogs tested | Dogs vomiting | % |
|------------------------|-------------|---------------|-------|
| 0.5 | 7 | 1 | 14.3 |
| 1.0 | 7 | 0 | 0 |
| 2.0 | 7 | 1 | 14.3 |
| 4.0 | 7 | 4 | 57.1* |
| 8.0 | 7 | 7 | 100** |
| 0 (Water) | 7 | 0 | 0 |

*p<0.05

**p<0.01

evaluated using Fisher's Direct Probability Test, calculating percent significance between the control group and each of the TAP groups. These calculations illustrated the emesis-inducing effect of TAP at the 5.0% significance level for the 4.0 mg/10 ml/animal group and at the 1.0% significance level for the 8.0 mg/10 ml/animal group. Table 5 lists the effect of TAP on the latency of emesis in beagle dogs treated with 4.0 or 8.0 mg TAP/10 ml/animal. The mean latency period in the 4.0 mg/10 ml/animal group was 15 min and 15 sec, with a standard error of 4 min and 16 sec. In the 8.0 mg/10 ml/animal group, it was 16 min and 17 sec, with a standard error of 5 min and 7 sec. Using the t-test, no significant difference was detected in the latency of emesis between these two dosage groups. The overall latency period for both groups combined was 15 min and 54 sec, with 95% confidence limits of 8 min and 11 sec to 23 min and 38 sec.

Table 5. Effect of TAP on Latency of Emesis in Beagle Dogs

| 8mg/10ml/animal | | 4mg/10ml/animal | |
|-----------------------------------|---------------|-----------------------------------|---------------|
| Dog No. | Latency(min.) | Dog No. | Latency(min.) |
| 31 | 14 | 3 | 8 |
| 32 | 9 | 4 | 16 |
| 33 | 8 | 5 | 10 |
| 34 | 32 | 6 | 27 |
| 35 | 6 | $\bar{x} \pm SE$ 15:15 \pm 4:16 | |
| 36 | 39 | | |
| 37 | 6 | | |
| $\bar{x} \pm SE$ 16:17 \pm 5:07 | | | |

Mean:15min.54sec.(8:11-23:38)

The numbers in parenthesis indicate the 95 per cent confidence limits.(min.:sec.)

Experiment II. Repetitive TAP Administration

Tables 6 and 7 list the results obtained from repeated administration of TAP. TAP was administered 7 times, at 1-week intervals, at the established threshold dosages of 8.0 mg/10 ml/animal or 4.0 mg/10 ml/animal, respectively. The 8.0 mg/10 ml/

Table 6. Reproducibility of TAP Emesis, Using the Threshold Dosage in Beagle Dogs

| TAP dosage (mg/10ml/animal) | Dog No. | Week | | | | | | |
|-----------------------------|---------|------|----|----|----|----|----|----|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 8 | 32 | 9 | 14 | 27 | 11 | 10 | 7 | 11 |
| | 34 | 32 | 32 | 14 | n | 29 | 65 | 13 |
| | 35 | 6 | 5 | 5 | n | 26 | 23 | 10 |
| | 36 | 39 | 5 | 10 | 9 | 19 | 7 | 12 |

Values are latency (min.), n : no vomiting

Table 7. Reproducibility of TAP Emesis, Using the Threshold Dosage in Beagle Dogs

| TAP dosage (mg/10ml/animal) | Dog No. | Week | | | | | | |
|-----------------------------|---------|------|----|----|----|----|----|----|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 4 | 3 | 8 | n | 5 | n | 38 | 15 | 41 |
| | 4 | 16 | 38 | 15 | 41 | 55 | 5 | 34 |
| | 5 | 10 | 33 | 24 | 7 | n | 14 | n |
| | 6 | 27 | n | 18 | 24 | 40 | 11 | 32 |

Values are latency (min.), n : no vomiting

animal group exhibited the emetic response all 7 trials in 2 of the dogs and in 6 out of 7 times in the other dogs. However, in the 4.0 mg/10 ml/animal group, emesis was repeated all 7 times for 1 dog, 6 of 7 times for 1 dog and 5 times for the other two dogs. These results indicate that the repeated administration of TAP did not modify the observed emetic responses or prolong the latency of emesis in any of the animals tested.

Experiment III. TAP's Active Mechanism

To study the active mechanism of TAP in dogs, the chemoreceptor trigger zone was inhibited by pretreatment with chlorpromazine (CPZ) before the TAP was administered. The results are shown in Table 8. Also iv injection of apomorphine (200 ug/animal) caused vomiting in 100% of the animals tested. The apomorphine-induced emesis was completely inhibited when the animals were pretreated with 2.0 mg/kg of CPZ. TAP, with an orally administered dose of 8.0 mg/10 ml/animal, also induced vomiting in all of the animals tested. However, despite pretreatment with 2.0 mg/kg of CPZ, TAP-induced emesis was observed in 8 of 11 dogs (incidence of emesis, 72.7%). Also there was no significant difference in the period between TAP administration and the onset of emesis between the TAP and CPZ + TAP groups (X^2 Test, $p=0.05$), illustrating the fact that CPZ does not inhibit TAP-induced emesis.

Table 8. Effect of CPZ on TAP-Induced Emesis

| Group | Dosage | Dogs tested | Dogs vomiting | % |
|-----------------|------------------------------------|-------------|---------------|-----------------|
| Apomorphine | 200 ^a | 11 | 11 | 100 |
| CPZ+Apomorphine | 2.0 ^b +200 ^a | 11 | 0 | 0 ^{ss} |
| TAP | 8 ^c | 11 | 11 | 100 |
| CPZ+TAP | 2.0 ^b + 8 ^c | 11 | 8 | 72.7 |
| Water(10ml) | - | 11 | 0 | 0 |

a:ug/animal(iv), b:mg/kg(sc), c:mg/animal(po)

CPZ : Chlorpromazine, TAP : Triazolopyrimidine

** :p<0.01

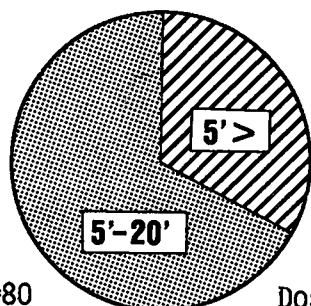
Experiment IV. Frequency of TAP-Induced Emesis in Mongrel Dogs

Table 9 and Fig 1 list the results obtained when 80 adult, mongrel dogs were treated with 8.0 mg/10 ml/animal TAP doses, which were determined the effective emetic dosage for beagle dogs in Experiment I. In this group of mongrel dogs, vomiting occurred from 3 to 19 min after TAP administration, with a 100% incidence of emesis. Vomiting occurred in 32.5% of this group within 5 min and 67.5% from 5 to 20 min. The mean latency of emesis was 5 min and 55 sec with a 95% confidence limits of 5 min and 21 sec to 6 min and 29 sec.

Table 9. Latency of TAP-Induced Emesis in Minutes (Adult Mongrel Dogs)

| Dog No. | Sex | B.W. (kg) | Latency (min.) | Dog No. | Sex | B.W. (kg) | Latency (min.) |
|---------|-----|-----------|----------------|---------|-----|-----------|----------------|
| 101 | F | 6 | 6 | 141 | F | 12 | 9 |
| 102 | F | 6 | 6 | 142 | F | 13 | 5 |
| 103 | F | 6 | 6 | 143 | F | 6 | 5 |
| 104 | F | 7 | 6 | 144 | F | 7 | 5 |
| 105 | F | 6.5 | 3 | 145 | M | 12 | 7 |
| 106 | F | 6 | 4 | 146 | M | 7 | 6 |
| 107 | F | 6 | 5 | 147 | M | 10 | 6 |
| 108 | F | 7 | 6 | 148 | F | 11 | 1 |
| 109 | F | 8 | 14 | 149 | F | 14 | 1 |
| 110 | F | 7 | 8 | 150 | F | 12 | 3 |
| 111 | F | 6.5 | 6 | 151 | F | 8 | 4 |
| 112 | F | 9 | 3 | 152 | F | 10 | 4 |
| 113 | F | 10 | 5 | 153 | F | 9 | 4 |
| 114 | F | 6 | 4 | 154 | F | 8 | 4 |
| 115 | F | 6 | 7 | 155 | F | 8 | 4 |
| 116 | F | 6.5 | 7 | 156 | F | 8 | 4 |
| 117 | F | 6 | 5 | 157 | F | 7 | 5 |
| 118 | M | 10 | 8 | 158 | F | 10 | 7 |
| 119 | F | 9 | 6 | 159 | F | 9 | 4 |
| 120 | F | 7 | 6 | 160 | M | 10 | 4 |
| 121 | F | 7 | 6 | 161 | M | 6 | 4 |
| 122 | F | 8 | 6 | 162 | M | 6 | 4 |
| 123 | F | 8 | 7 | 163 | F | 6.5 | 5 |
| 124 | F | 7 | 4 | 164 | F | 8 | 3 |
| 125 | F | 10 | 8 | 165 | F | 8 | 3 |
| 126 | M | 8 | 7 | 166 | F | 9 | 7 |
| 127 | M | 9 | 7 | 167 | F | 8 | 7 |
| 128 | M | 9 | 7 | 168 | F | 8 | 5 |
| 129 | F | 10 | 8 | 169 | F | 12 | 6 |
| 130 | F | 8 | 9 | 170 | F | 7 | 6 |
| 131 | M | 7 | 3 | 171 | F | 12 | 9 |
| 132 | F | 7 | 5 | 172 | M | 12 | 3 |
| 133 | F | 6.5 | 4 | 173 | M | 11 | 3 |
| 134 | F | 7.5 | 9 | 174 | M | 8 | 5 |
| 135 | F | 10 | 7 | 175 | F | 7 | 6 |
| 136 | M | 9.5 | 5 | 176 | F | 7 | 6 |
| 137 | M | 9 | 5 | 177 | F | 12 | 8 |
| 138 | M | 11 | 5 | 178 | F | 12 | 10 |
| 139 | M | 7.5 | 9 | 179 | M | 8 | 19 |
| 140 | M | 9 | 8 | 180 | M | 12 | 4 |

All 80 dogs exhibited emesis when 8mg/10ml/animal of TAP was administered.



N=80
Dose: 8mg/animal
Vomiting Response: 100%
Latency (min.:sec.): 5:55±0:17 (mean±SE)

Figure 1. TAP-Induced Emesis in Mongrel Dogs.

DISCUSSION

The effective emetic dose established for TAP in the beagle dogs that we examined in Experiment 1 was 8.0 mg/10 ml/animal ($p \leq 0.01$) and 4.0 mg/10 ml/animal ($p \leq 0.05$). Compared to earlier reported effective emetic doses for other emetic drugs, such as tartar emetic (40-80 mg/10 ml/animal) (12), copper sulfate (50-100 mg/100 ml/animal) (12) and TKPP (4,800 mg/animal, 20% solution) (13), TAP can be expected to produce emesis effectively at a far lower dose. Kayashima et al (23) attempted repetitive oral administration using copper sulfate in dogs. They found that none of the animals tested had emetic responses more than twice in succession and attributed this non-recurrence of emesis to an elevation of the animals threshold dose. However, in our study, the repeated administration of TAP was successful in inducing emesis more than twice in all of the dogs tested, with no prolongation or shortening of the latency period. This strongly suggests that, unlike copper sulfate, the repeated ingestion of TAP does not lead to an elevation of the threshold emetic dose.

Apomorphine is known to act on the central system. In our series of experiments, pretreatment with CPZ inhibited the emetic action of apomorphine, but CPZ pretreatment did not affect the emetic action of TAP. These results indicate that, unlike apomorphine, TAP does not act on the central system, but peripherally on the gastrointestinal mucosa.

The effective emetic dose of TAP in beagle dogs, 8.0 mg/10 ml/animal, caused emesis in 100% of the mongrel dogs tested as well. Kayashima et al (23) and Jonouchi et al (12) found remarkable individual variability in the sensitivity to copper sulfate in their studies with mongrel dogs. This adds support to the superior effectiveness of TAP as an emetic, compared to copper sulfate. On the other hand, Akahori et al (13) reported that the emetic effects of TKPP vary significantly, depending on the concentration and demonstrates an adequate emetic effect at dosages of 4,800 mg/animal in a 20% solution or higher. This indicates that TAP is preferable to TKPP, due to its having a much lower effective emetic dosage and easier mixing with agricultural chemical compounds.

In conclusion, TAP is considered to have many superior characteristics when compared to other emetic compounds, as illustrated in our research with beagle and mongrel dogs.

REFERENCES

1. Almog C and Tal E: Death from paraquat after subcutaneous injection. Br Med J 3:721, 1967.

2. Bullivant CM: Accidental poisoning by paraquat: Report of two cases in man. *Br Med J* 1:1272-1273, 1966.
3. Fennelly JJ, Gallagher TJ and Carroll RJ: Paraquat poisoning in a pregnant woman. *Br Med J* 3:722-723, 1968.
4. Kuhara H, Wakabayashi T, Kishimoto H, Hayashi K, Suti T and Matunaga T: Five autopsy cases of paraquat poisoning. *Nippon Nohson Igakkai Zasshi*, 26:647-656, 1977, (in Japanese).
5. Ueda K and Hiraki K: Poisoning of Pesticide. Nankodo, Tokyo, 173, 1978.
6. Nishimura H, Nishimura N and Oshima H: Experimental studies on the toxicity of herbicide paraquat (Report 2). *JAMUA* 7:197-201, 1979 (in Japanese).
7. Oshima H, Nishimura H and Nishimura N: Experimental studies on the toxicity of herbicide paraquat (Report 1). *JAMUA* 7:98-103, 1979 (in Japanese).
8. Preopoulos DG, Soyannwo MAO, Sinniah R, Fenton SSA, McGeown MG and Bruce JH: Acute renal failure in case of paraquat poisoning. *Br Med J* 1:749-750, 1968.
9. Sugaya T and Wakatuki T: An inquiry of clinical cases of pesticide poisoning in Japan (during 1978). *Nippon Nohson Igakkai Zasshi* 28:452-453, 1979, (in Japanese).
10. Yamashita K, Aoyama S, Ikuta S, Miyake T and Arima K: An autopsy case of intentional poisoning by the herbicide (paraquat); Comment on comparison between the injury by insecticide and herbicide. *Nippon Nohson Igakkai Zasshi* 23:27-38, 1973, (in Japanese).
11. Yoneyama M, Kainuma T and Takeuchi I: An acute poisoning by the new herbicide (paraquat). *Nippon Igi Sinho* 2374:32-34, 1969, (in Japanese).
12. Jonouchi S, Masaoka T and Akahori F: Vomiting tests of tartar emetic and cupric sulfate in mongrel dogs and beagles. *Bull Azabu Univ Vet Med* 1:289-296, 1980 (in Japanese).
13. Akahori F, Masaoka T and Akiyama E: Determining the effective emetic dosage of tetra-potassium pyrophosphate (TKPP) in dogs. *J Toxicol Sci* 7:151-158, 1982.
14. Weaver JE and Griffith JF: Induction of emesis by detergent ingredients and formulations. *Toxicol Appl Pharmacol* 14:214-220, 1968.
15. Rose MS: The concentration of pp796 required to produce emesis in experimental animals and an estimation of the emesis dose in man. Report No: CTL/R/390, 1976.
16. Rose MS: The effect of administration of an emetic (pp796) on paraquat toxicity in dog and monkey. Report No: CTL/R/391, 1976.
17. Takizawa T: Nomogram for obtaining a necessary, Minimum sample size, IV. When the distribution of sample proportion is made to approximate F-distribution. *Bull Nat Inst Anim Health*, 73:43-49, 1976.
18. Yamauchi C: An outline of experimental dog in USA. *Exp Anim* 20:173-177, 1971.
19. Cahill JI, Jones BR and Cooper BS: Hydergine as an emetic for dogs. *NZ vet J* 29:133-134, 1981.
20. Dipalma JR: *Drill's Pharmacology in Medicine*, McGraw-Hill Book Co, NY, 338, 1971.
21. Rossoff SI: *Handbook of veterinary drugs*. Springer Pub Co, NY, 23, 1974.
22. Moeschin S: *Poisoning (Diagnosis and Treatment)*. Grune & Stratton, NY and London, 273, 1974.
23. Kayashima N and Hayama T: Reproducibility of copper sulfate emesis by oral threshold dose in dogs. *Folia Pharmacol Japon* 71:161-173, 1975.

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circulation, however, increased gradually over 60 minutes. The absorption was both concentration and pH-dependent, i.e., the lower the pH and the higher the intraluminal concentration, the higher the rate of appearance of Al into the circulation.

74 ~~X~~ THE FREQUENCY AND PROBLEMS OF PARAQUAT POISONING IN EUROPE, AS EXPERIENCED BY THE POISON CONTROL CENTRES. ~~X~~
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Poisonings by the herbicide paraquat have been a problem for many years. Paraquat is a very toxic substance, there is no really efficient therapy and poisoning is very often fatal. The World Health Organization has been preparing an "Environmental Health Criteria Document" on paraquat and the problem of paraquat poisonings was therefore again discussed within the European Association of Poison Control Centres. The question was whether there had been any decrease in the number of poisonings following stricter official control and the addition of an emetic and staining agent to commercial preparations. As Secretary of the EAPCC the author surveyed different poison control centres in Europe, asking if they had experienced any decrease in the number of poisonings from paraquat in their country or region, and to give their view on the problem. 37 centres answered the inquiry. In France and West-Germany a national report on paraquat poisonings had been prepared. No centre had experienced any real decrease in the total number of paraquat poisonings, although accidental poisonings may be a little less frequent in some countries at present. The majority of centres were very concerned about paraquat because of its toxicity and the lack of an efficient therapy in cases of poisoning. Some proposed changes in the formulation of paraquat preparations and suggested less concentrated liquid preparations or solid preparations only.

75 A NEW STATISTICAL APPROACH TO THE PROGNOSTIC SIGNIFICANCE OF PLASMA PARAQUAT CONCENTRATIONS.

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76 DENTURE CLEANER INGESTION.

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In order to assess the hazard arising from ingestion of denture cleaners, a prespective survey of all cases referred during the two years 1982-1983 was undertaken. By April 1984,

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DRAFT

**EFFECT OF THE ADDITION OF AN EMETIC TO PARAQUAT FORMULATIONS
ON ACUTE POISONING IN MAN**

HART, T. B. and WHITEHEAD, A.

SUMMARY

In an effort to minimise the risk of accidental poisoning by ingestion of paraquat formulations, the manufacturer has added an emetic to the products containing paraquat. The addition was shown in animal models (dog and monkey) to increase the potentially lethal oral dose of paraquat by a factor of 3-5. This survey was designed specifically to examine the effects of this addition on paraquat poisoning in man.

640 cases of paraquat poisoning were reviewed, out of which 230 patients had swallowed the product containing emetic. In those patients swallowing the 'emeticised' product, 97% vomited spontaneously, compared with 65% of a retrospective control group who had swallowed 'non-emeticised' product. The speed of onset of vomiting as a result of the emeticised product was usually within 30 minutes of ingestion.

Comparison of the group of patients poisoning with 'emeticised' product with another retrospective control group involving 'non-emeticised' product shows that the mortality of paraquat poisoning has fallen from 84% to 64% for liquid formulations and from 21.5% to 12% for solid formulations following introduction of the emetic. It is unlikely that improved treatment or smaller doses of paraquat swallowed have caused this reduction, but it is difficult to conclude with any degree of certainty that the emetic addition is solely responsible.

As the emetic has been shown to reduce the toxicity of paraquat in animal models and it is an effective, reliable emetic in man, even in the presence of paraquat, this reduction in mortality of paraquat poisoning may well be due, in part, to the addition of emetic. This addition has not been shown to be associated with any serious adverse effects associated with the use or abuse of paraquat and as it may protect cases of accidental poisoning with paraquat, it is probably better to add emetic to paraquat formulations than to exclude it.

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INTRODUCTION

X Paraquat, (1,1 dimethyl-4-4'bipyridillium) was discovered as a herbicide in the 1950's and first sold as a product in 1962. The most common formulation of paraquat available worldwide is Gramoxone, an aqueas solution containing 200g per litre of paraquat ion. This formulation is now sold in over 130 countries throughout the world. In the United Kingdom, paraquat is also sold as a lower strength solid formulation, Weedol or Pathclear, containing 2.5% w/w paraquat and 2.5% w/w diquat, for use by the amateur gardener.

Although paraquat has been shown to be safe in normal use^{1,2,3,4,5}, regrettably its abuse, associated invariably with ingestion of the product, has been responsible for a number of fatalities. In the United Kingdom, the vast majority of abuse arises from suicide⁶ and the incidence of fatal accidental poisoning remains very low. Nevertheless in order to further minimise the risk of accidental fatality from swallowing, the manufacturer has added several chemicals to the formulations. Two of these, a pyridine-based chemical designed to produce an odour and a blue dye have been added to warn people, who may be about to drink concentrated liquid paraquat formulation. The third is an emetic, which has been added to the formulation as a built in first-aid measure.

Prior to the addition of this emetic, a number of selection criteria had to be met. These included:-

1. The emetic should be sufficiently rapid in action.
2. The emetic must be effective, in the presence of paraquat, in removing toxicant from the stomach and increasing the potential lethal oral dose.
3. The emetic must not interfere with the safety of paraquat to man and his environment, associated with normal use.
4. The emetic must be physically compatible and miscible with paraquat in the formulations and must not interfere with the herbicidal action of paraquat.

7 - codenamed PP796, was chosen as the emetic, because during its development as a drug for obstructive airways disease, it was found to be a very potent emetic in man with a rapid onset of action. A single oral dose of 5mg of emetic in an adult was considered sufficient to cause vomiting. It was also considered preferable as it was centrally acting, as opposed to an irritant or peripherally acting emetic. Irritant chemicals can enhance paraquat absorption across membranes. Finally, it fulfilled all the above selection criteria, particularly the second criterion. In animal models (dog and monkey) the potential lethal dose was increased by a factor of 3-5 fold⁷ in the presence of emetic.

X As a result, this emetic was introduced into paraquat formulations at a concentration of 0.05% w/v, or w/w equivalent to 5mg emetic in 10ml of Gramoxone or 1.5 sachets of Weedol/Pathclear. Thus the emetic was added at a concentration that would cause voimiting should the minimum protential lethal dose of paraquat formulation be swallowed.

The aim of this paper is to review the information from human cases of paraquat poisoning to determine how applicable the animal data is to man. In particular to assess:-

1. How effective the emetic is, in the presence of paraquat, in causing vomiting in man?
2. What effect, if any, has the emetic had on the mortality of paraquat poisoning?
3. What adverse effects, if any, has the emetic addition had?

METHODS

1. Patient Records

The study involved detailed questionnaire and follow-up of patients in the United Kingdom as described by Hart and Bramley⁶ (1983). In particular, effort was made to determine details of the product involved and whether or not the emetic was present. The latter was achieved by one or more of several methods, including identification of the product label (Figure 1), analysis of the original product for presence of emetic and analysis of the patient's urine for the presence of emetic metabolite.

Analysis of the patient's urine for emetic metabolite is a useful means of confirming emetic involvement, but cannot be used to determine its absence. A negative result may be due to emetic absence, but could also arise in patients who have swallowed low doses of paraquat and emetic, in which case emetic metabolite levels may be undetectable or in patients, whose urine was collected too late. (emetic metabolite is usually undetectable in urine taken after 48 hours of ingestion).

2. Control Group

As this study was conducted after introduction of the emetic into United Kingdom formulations and it is extremely difficult to prove absence of emetic involvement, a retrospective control group of paraquat poisoning cases, not involving the emetic, was used.

3. Analysis

The presence of emetic in the original product was analysed by ■

Urine analysis for presence of the emetic metabolite was done using ■

RESULTS

1. General Statistics

The survey has reviewed a total of 640 cases of proven paraquat poisoning out of which 11 were fatal and 629 non fatal. The majority of these cases (511 of the total) were associated with suicidal ingestion and 11 of all fatalities were suicides. Paraquat poisoning is more common in males, 511, than females 11 and poisoning in children is rare (11 cases, all non-fatal).

2. Emetic Cases

The emetic was confirmed as being involved in 230 cases (36% of the total) and in 78 of these, the emetic metabolite was detected in the patient's urine.

3. Effectiveness of Emetic in Causing Vomiting

Only those patients swallowing more than 10ml of Gramoxone or 1.5 sachets of Weedol/Pathclear were considered. Of the 69 patients, who met the above criterion and on whom sufficient information was available, 67 (97%) vomited spontaneously. Spontaneous vomiting is defined, in this context, as vomiting solely due to ingestion of the product.

Figure 2 illustrates the speed of onset of spontaneous vomiting. The majority of patients (64%) vomit within 30 minutes of ingestion and 94% vomit within 1 hour of ingestion.

4. Effect of Addition of Emetic to Paraquat Formulations on Mortality of Poisoning

Table 1 summarised the mortality statistics for patients who have ingested 'non-emeticised' paraquat formulations. These are considered under two categories - low strength solid formulations (Weedol/Pathclear) and concentrated liquid formulations (Gramoxone/Dextrone). Similarly Table 2 summarises the mortality statistics for paraquat formulations, containing emetic, considered in the same categories as in Table 1.

The mortality rate for poisoning with solid and liquid paraquat formulations not containing emetic is 21.5% and 84% respectively, but for similar formulations containing emetic, it is considerably lower with a 12% and 64% mortality rate respectively.

TABLE 1

MORTALITY OF NON-EMETIC PARAQUAT POISONING

| | Fatal | Non-Fatal | % Mortality |
|----------------------------|-------|-----------|-------------|
| <u>Solid Formulations</u> | | | |
| Weedol | 38 | 131 | 22.5) |
| Pathclear | 1 | 11 | 8.3) 21.5 |
| <u>Liquid Formulations</u> | | | |
| Gramoxone | 119 | 18 | 87) |
| Dextrone | 4 | 5 | 44) 84 |

TABLE 2

MORTALITY OF EMETIC PARAQUAT FORMULATIONS

| | Fatal | Non-Fatal | % Mortality |
|----------------------------|-------|-----------|-------------|
| <u>Solid Formulations</u> | | | |
| Weedol | 14 | 116 | 11) |
| Pathclear | 5 | 25 | 17) 12 |
| <u>Liquid Formulations</u> | | | |
| Gramoxone | 40 | 20 | 67) |
| Dextrone | 1 | 3 | 25) 64 |

TABLE 3

POTENTIAL LETHAL ORAL DOSE OF PARAQUAT (HUMAN)

| Dose of Paraquat Ion Reported as being Swallowed | No Fatal | No Non-Fatal | % Mortality |
|--|-------------|-----------------|-------------|
| <2 g | 10 | 93 | 9 |
| 3 to <5 g | 29 | 23 | 56 |
| 5 to <10g | 18 | 2 | 90 |
| 10g or more | 43 | 0 | 100 |

TABLE 4

PARAQUAT DOSE PROFILE
NON-EMETIC/EMETIC GROUPS

| Dose of Paraquat Swallowed (GM. PQ. ION) | Number of Patients (as % of total) swallowing | | | |
|--|--|--------|---------------------|--------|
| | Solid Formulations | | Liquid Formulations | |
| | Non-Emetic | Emetic | Non-Emetic | Emetic |
| <2 | 81% | 84% | 6 | 15 |
| 2 - <5 | 16% | 15% | 9 | 26 |
| 5 - <10 | 3% | 1% | 25 | 26 |
| 10+ | 0% | 0% | 60 | 33 |
| <hr/> | | | | |
| TOTAL NO OF CASES | 145 | 352 | 110 | 176 |

DISCUSSION

The potential lethal oral dose of paraquat in man, has often been cited as 10-15ml of Gramoxone, equivalent to 3g of paraquat ion. We can confirm that this dose is more or less correct by studying doses said to have been ingested by patients. All cases refer to ingestion of non-emeticised paraquat and these are summarised in Table 3. As can be seen, increasing doses of paraquat are associated with higher mortalities. Furthermore, doses of 2 to 5g of ingested paraquat, equivalent to between 10 and 25mls of Gramoxone are associated with about 50% mortality. From the above, we can conclude that the potentially lethal oral dose of paraquat to man is between 2 and 5g of ion equivalent to 10 to 25ml of Gramoxone.

The addition of emetic to paraquat formulations has been shown, using animal models, to increase the potential lethal oral dose by a 3-5 fold factor. If the same is true for man, then the potentially lethal oral dose of 15ml should be increased to approximately 50ml of Gramoxone. Such a dose is rather more than a mouthful (approximately 30-40mls) and should cover those individuals who swallow Gramoxone accidentally. Suicides with paraquat may swallow much more than 50ml Gramoxone and therefore the emetic in these cases is unlikely to be of significant benefit.

The addition of the emetic to paraquat formulations produces a rapid onset of vomiting in the majority of patients (97%) who swallow the product. Paraquat itself is irritating to the gastro-intestinal tract and may produce vomiting. Howard (1979) reviewed 68 cases of paraquat poisoning involving non-emeticised product. About 50-60% of this group vomited spontaneously, but analysis of the original data shows that in 45 cases swallowing more than 10ml of Gramoxone or 1.5 sachets of Weedol or Pathclear, that is similar in doses as the 'emeticised' formulation cases involved, 65% of the patients vomited spontaneously. Hence it can be concluded that the addition of emetic to paraquat formulations has markedly improved the reliability of induction of vomiting. In most cases the addition of emetic has led to an early onset of vomiting.

Comparison of tables 1 and 2 shows that since the addition of the emetic, the mortality of both the solid and liquid formulations of paraquat has fallen from 21.5% to 12% for solid formulations and from 84% to 64% for liquid formulations. The difference in mortality rates between solid and liquid formulations is undoubtedly due to the different concentrations and therefore acute toxicities of the two formulation types. However it is difficult to positively conclude that the reduction in mortality from 84% (liquid) and 21.5% (solid) for 'non-emeticised' formulations to 64% (liquid) and 12% (solid) for 'emeticised' formulations, is solely due to the addition of emetic.

A number of factors will influence the mortality statistics and we have tried to take into account as many of these as possible in forming our conclusions. One factor, which is important, is the treatment given to patients in the 'non-emeticised' and 'emeticised' groups. The treatment for a paraquat poisoning was developed and made available to doctors as early as 1974. Since then it has changed very little. The majority (73%) of the patients in the 'non-emeticised' group occurred after this date, so that treatment is unlikely to be a influencing factor on the mortality rates.

Another possible factor is that the patients in the two groups may have on average swallowed different doses of paraquat. Table 4 shows the type of doses of paraquat swallowed by patients according to the type of formulation involved and whether or not it contained emetic. In the case of the solid formulations, there is very little difference between the two groups, but rather more cases (as a percent of the total) swallowed smaller doses of emeticised liquid formulation compared with the non-emeticised product. It is unlikely that these differences have influenced the reduction in mortality from paraquat poisoning, because the reduction in poisoning mortality with solid formulations containing emetic is far greater (44%) than that involving the liquid formulations (24% reduction).

In spite of the above, it is not possible to account for every influencing factor, and therefore caution must be used when drawing conclusions from the data. However, in view of the fact that the emetic addition has been shown to lower the toxicity of paraquat in animal models and has been shown to cause reliable and rapid onset of vomiting in man, it is likely that this reduction in paraquat poisoning mortality may be due in part to the presence of emetic.

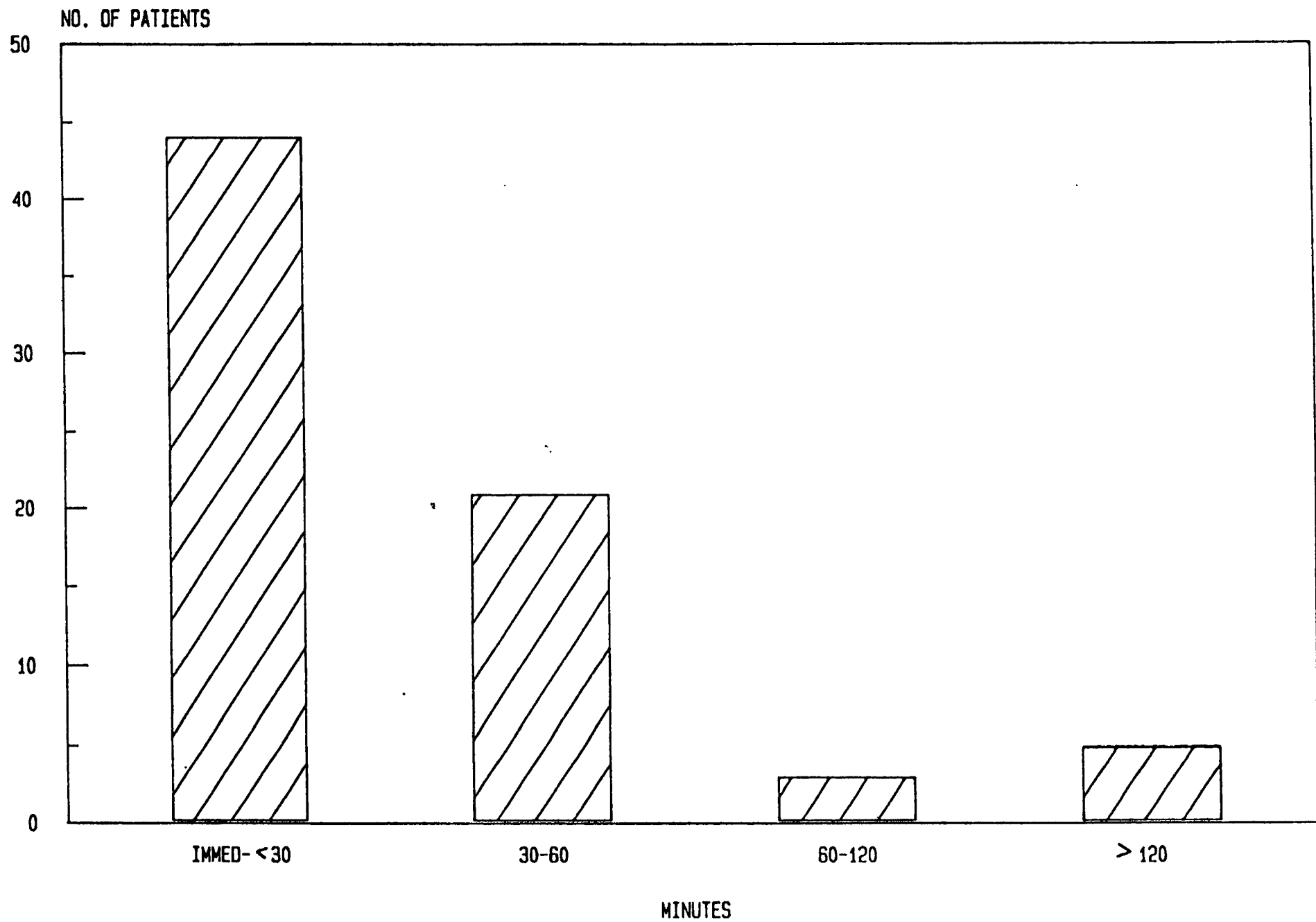
The survey showed very little evidence of serious untoward effects associated with use or abuse of the emeticised paraquat formulations. The occasional instance of persistent vomiting and fluid and electrolyte imbalance was attributed to the emetic, but these were very few in number. Therefore on the basis that the emetic addition may well help protect accidentally poisoned patients with paraquat and is unlikely to be harmful, we believe it is better to have the emetic in the formulations than to exclude it.

TBH/MN
11.9.84.
TBH2

REFERENCES

1. Swann, A.A.B. (1969)
Exposure of Spray Operators to Paraquat.
Brit. J. Ind. Med. 26 322-329.
2. Hearn, C.E.D., and Keir, W. (1971)
Nail Damage in Spray Operators Exposed to Paraquat.
Brit. J. Ind. Med. 28 399-403.
3. Howard, J.K. (1979).
A Clinical Survey of Paraquat Formulation Worker.
Brit. J. Ind. Med. 36 220-223.
4. Howard, J.K. (1980)
Paraquat : A Review of Worker Exposure in Normal Usage.
J. Soc. Occup. Med. 30 6-11.
5. Howard, J.K., Sabapathy, N.W., and Whitehead, P.A. (1981).
A Study of the Health of Malaysian Plantation Workers with Particular
Reference to Paraquat Spraymen.
Brit. J. Ind. Med. 38 110-116.
- * 6. Hart, T.B. and Bramley, A. (1983).
Paraquat Poisoning in the United Kingdom.
Human Toxicology 2 417.
7. Rose, M.S. (1976).
The Effect of Administration of an Emetic (PP796) on Paraquat Toxicity
in Dog and Monkey.
ICI Central Toxicology Laboratories - internal report.
8. Howard, J.K. (1979).
Recent Experience with Paraquat Poisoning in Great Britain.
A review of 68 cases.
Vet. and Human Tox. 21 suppl. 213-216.
9. 'The Treatment of Paraquat Poisoning - A Guide for Doctors'.
ICI Booklet Publication.

EMETIC - SPEED OF ACTION



From: L L Smith

14 September 84

To: Alison Fenna
Bruce Woolen
Mike Godley
I F H Purchase
S E Jagers

LLS/DLB

Please forward comments on this draft document as soon as possible.

L L SMITH

FROM: M J Godley
TO: Dr L L Smith

MJG/KH

cc Mrs A Fenna
Dr B Woollen
Dr I F H Purchase
Dr S E Jagers

25th September 1984

COMMENTS ON DRAFT DOCUMENT ENTITLED 'EFFECT OF THE ADDITION OF AN EMETIC TO
PARAQUAT FORMULATIONS ON ACUTE POISONING IN MAN' BY T B HART & A WHITEHEAD

1. There are several cases of apparent differences in 'total' counts of cases. Undoubtedly this is often due to not all the information being available in all cases to enable inclusion in all tables by various factors. However, I feel some comment to this effect might allay fears that the numbers are 'incorrect'. Others may be the result of my misunderstanding the figures in which case perhaps more comprehensive table headings would resolve, eg:
 - a) pg 5 para 2 '230 cases' compared to pg 6 Table 2 with a total of 224 cases.
 - b) Does Table 3 refer to solid and liquid formulation or solid only? Pg 8 line 8 says all cases but total in Table 3 is 218 and in Table 4 145 + 110 = 255.
 - c) Pg 1 para 2 '640 cases' compared to a total of 783 in Table 4.
2. Has the balance of solid to liquid formulation changed (Tables 1 and 2)?
'Non-emetic' (older) cases solid 181 liquid 146 (ratio 1.2:1)
'Emetic' (newer) cases solid 160 liquid 64 (ratio 2.5:1)
Is the identification of formulation containing emetic 'easier' if solid rather than liquid?
3. Table titles 1 and 2 'poisonings' compared to 'formulations'.
4. Should second lowest dose category in Table 3 read '2 to <5g' (not '3 to <5g') as in Table 4? This would correspond with text statement on pg 8 line 6 'doses of 2 to 5g ... associated with about 50% mortality'.
5. I have checked by crude methods the numerical support for some of the statements made ie
 - a) Pg 5 last para: 12% and 64% being 'lower' than 21.5% and 84% - justified.
 - b) Pg 9 1st para: 44% reduction 'greater' than 24% reduction - justified.
 - c) Pg 8 para 3: increased incidence of vomiting 67/69 compared to 45/60 - justified.

6. The paper acknowledges that a number of other factors may influence the mortality data (pg 8 and 9). The references to 'treatment for paraquat poisoning' and possible differences pre-1974, made me interested to know the years applying to the two data bases 'emetic' and 'non-emetic'. The conclusion that differences in 'treatment for paraquat poisoning' are unlikely to be an influencing factor on mortality rates is a little strong. In the case of liquid formulations it is undoubtedly reasonable to assume that this factor could not 'explain' the reduced mortality but in the cases of solid formulations even though 73% of the 'non-emeticised' group occurred after 1974 it is possible (by applying a 47% mortality rate pre-1974 and a 12% mortality rate post-1974 - for both emetic and non-emetic groups)- for the reduced mortality rates observed to have been totally the result of 'improved' treatment.
7. The phrase 'potential lethal dose' is unclear to me. It is not quantitatively defined and appears on pg 8 para 1 to be more related to the incidence of 50% mortality ('2 to 5g ... associated with about 50% mortality') than to what I intuitively expected, ie the lowest dose at which lethality becomes a real possibility. I have difficulty reconciling the statement that 'the potentially lethal dose to man is between 2 and 5 g ...' (pg 8 line 8) when Table 3 clearly shows deaths at doses of <2g. (I acknowledge the uncertainties associated with the dose estimates in this Table.) The implication of the observation that following the introduction of the emetic the potentially lethal dose is '... rather more than a mouseful ...' (pg 8 line 4 para 2), ie that a mouthful is not potentially lethal, seems unconvincing to me.
8. Finally I am concerned about the way in which the data in Table 3 might be abused.

For example assuming dose levels for each category of <2g (say 0.5g), 2g to <5g (say 4g) and 5g to <10g (say 8g) the application of a probit mortality dose-response relationship yields estimates of the human LD50 of 2.8g but more importantly of an LD1% (intuitively a 'potential lethal dose'?) of 0.14g.

I believe the data cannot 'prove' reduced mortality due to the emetic but on balance a reasonable judgement would be that it has made some contribution to this.



M J GODLEY

IMPERIAL CHEMICAL INDUSTRIES PLC
Central Toxicology Laboratory
ANALYTICAL CHEMISTRY SECTION REPORT

FROM: B.H. WOOLLEN

TO: T.B. HART

COMPOUND AND STUDY:

STUDY NUMBER:

COMPOUND NUMBER:

EMETIC PUBLICATION

| <u>Page</u> | <u>Para</u> | <u>Comment.</u> (M.S. = misspelling) |
|-------------|-------------|--------------------------------------|
| 2 | 1 | M.S. <u>aqueous</u> |
| | last | M.S. vomiting M.S. potential |
| 9 | 2 | M.S. vomiting |
| | 3 | M.S. emeticiser |

Analytical methods: -

product

--- by thin-layer chromatography

urine

-- by high performance liquid chromatography

(N.B. An acknowledgement of our analytical efforts would be appreciated)

Done

1.10.84

Anaesthesiology, General Surgery Department Clinic, Institute of Pharmacology, University of Padua and Institute of Forensic Medicine, University of Verona, Italy.

Toxicological, epidemiological and clinical information about acute intoxications admitted to the 114 hospitals in the Venetian region was collected. From computerized data (2,500,000) of roughly 5,000 cases over 2 years (78-79) poisoning agents were correlated with symptoms, management, laboratory findings and duration of hospital stay. Initial symptoms did not allow early correct diagnosis but the patients who came to hospital at least 6 hours after poisoning (45%) showed a number of signs that helped to make a good early diagnosis. The toxic removal (21%) is always associated with symptomatic management and shorter hospitalisation. The poisoning agents produce adrenergic reactions (>28%) and liver damages (>9%). Early symptoms influence the type of symptomatic management, standardized with a wide use of plasma expanders (16%) and corticosteroids (12%), and is discontinued as the clinical picture improves. The hospitalization time is independent of antidotal and removal treatment and is the same for any treatment. Often sedative drugs are given for sedative poisoning (!) but no duration change was observed. Initial management modifies the symptomatological picture, found in the literature, so that there is a decrease of the probability of a correct diagnosis from semeiological signs.

3 ACUTE DIQUAT INTOXICATION. INTEREST OF REPEATED TOXIN MONITORING IN URINE AND EVALUATION OF TUBULAR CELL INTEGRITY. P. Mahieu, Y. Bonduelle, A. De Cabooter, A. Bernard, A. Hassoun, J. Koenig and R. Lauwerys, Centre de Toxicologie Clinique, Cliniques Saint-Luc, Catholic University of Louvain, Louvain-la-Neuve, Brussels 1200, Belgium.

Published - J Toxicol-Clin Toxicol, 22, 363-369 (1984).

4 EFFECTS OF THE ADDITION OF AN EMETIC TO PARAQUAT FORMULATIONS ON ACUTE POISONING IN MAN.

A. Denduyts-Whitehead, T.B. Hart and G.N. Volans, National Poisons Information Service, Guy's Hospital, London, and ICI PLC, Plant Protection Division, Haslemere, Surrey.

The addition of an emetic to paraquat proved effective in reducing the oral LD50 in animals. In 1979, paraquat formulations in the UK were changed to incorporate the emetic. The NPIS monitored the presence of the emetic in paraquat products involved in acute poisoning and assessed its effects in man.

All cases of definite ingestion were reviewed. Particular effort was made to identify the product involved by obtaining

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details of the packaging as well as samples of the product, blood and urine for determination of the presence/absence of the emetic. Parameters used included: estimates of the amount of paraquat ingested, incidence of emesis, time to emesis, product verification and confirmation using three methods, and outcome. From a total of over 500 cases reported between 1979 and 1984 (March) the presence of the emetic was demonstrated or inferred in 120-150. Comparison of the findings in these cases with the findings in patients where non-emeticised paraquat was ingested were presented.

TOXICOKINETIC STUDY OF TRIAZOLAM IN ACUTE INTOXICATION.
 A. Jaeger, A. Lugnier, J. Kopferschmitt, M.L. Jaegle, P. Mangin, F. Fleisch and P.H. Sauder, Service de Réanimation Médicale et Centre Anti-Poisons - CHU - 67091 Strasbourg, France.

Triazolam is a new benzodiazepine with an ultra-short half-life of 1.5 to 5 hours. Triazolam kinetics were studied in 13 patients with acute intoxication: mean age 39.3 years (16 to 73); mean dose absorbed (DA) 16.9mg (7.5 - 60); mean lag time of the study 2 hours (1 - 3). Triazolam was analysed by HPLC in serum, urine and gastric fluid.

The peak serum level ranged from 9.2 to 142µg/l (mean 82.5) and the serum half-life from 82 to 505 min (mean 201). The amount removed by gastric lavage ranged between 0 and 3mg (mean 0.89 or 13% of the DA). The mean urinary excretion over a period ranging from 3 to 24 hours was 0.81 ± 0.66 mg (i.e. 4.8% of the DA) and the mean renal clearance was 30.7 ± 16 ml/min. The half time of urinary excretion varied from 1 to 5.8 hours (mean 2.9) in 6 cases. These results agree with the pharmacokinetic profile of triazolam: short elimination half-life, rapid absorption and urinary excretion, low levels of unchanged triazolam in urine. However, triazolam could be detected in serum and urine up to 14 hours after ingestion.

THE NEED FOR TOXICOLOGICAL ANALYSES IN THE ACUTE STAGE OF POISONING.

A. Hanson, H. Persson and N. Tryding, Department of Clinical Chemistry, Malmö Allmänna Sjukhus, Malmö; Swedish Poison Information Centre, Stockholm and Department of Clinical Chemistry, Central Hospital, Kristianstad, Sweden.

The need for acute toxicological analyses was discussed recently at a joint meeting arranged by The Swedish Poison Information Centre and The Swedish Society of Clinical Chemistry. A brief report will be given of the statements from this meeting.

In Sweden - a vast country with a small population - the distance between different hospitals may be long. As critically ill patients and blood samples cannot be transported too far in an

Paraquat Poisoning in the United Kingdom. A. Bramley & T. B. Hart. Poisons Unit, Guy's Hospital, London SE1 9RT and ICI Plant Protection Division, Fernhurst.

This is an interim report of a study jointly conducted by the National Poisons Information Service at Guy's Hospital, London and ICI Plant Protection Division. It was started in 1980 and has now been running two-and-half years.

The objectives of the study are to:

- 1 Examine in detail the incidence of paraquat poisoning in the United Kingdom.
- 2 Evaluate new and existing treatment methods for paraquat poisoning with particular emphasis on the use of Fuller's Earth and charcoal haemoperfusion.
- 3 Evaluate the effectiveness of an emetic added to paraquat formulations since 1977.

Following extensive media publicity of paraquat's toxicity, the number of paraquat poisonings increased in the period of time from the early 1970s to 1976. Since that year the number of cases, fatal and non-fatal, has remained more or less constant. This study shows that all fatal cases of poisoning resulted from ingestion of paraquat and the majority (95%) were associated with deliberate intent. According to the Office of Population and Censuses and Surveys fatal paraquat poisonings (suicides) now account for 1% of all suicide fatalities and 2½% of all suicide fatalities involving chemicals. Accidental fatalities from paraquat poisoning remain very low and account for 0.3% of all accidental fatalities involving chemicals.

The majority of the 262 (fatal 36%, non-fatal 64%) paraquat poisonings over the period reported in this study were male and adult. No children were involved in any fatal paraquat poisoning incidents. There appears to be no reproducible monthly variation in the number of poisonings involving either liquid (for professional users only) or solid (for the amateur gardener) formulations. Where information was available, patients poisoned with the liquid formulations were reported to have connection with the legitimate use of the product, indicating that the Poisons Regulations had not been violated.

Early treatment of paraquat poisoning (up to 12 to 24 hours) appeared to improve prognosis when the dose of paraquat ingested was relatively low. However, it has so far not been possible to demonstrate an improved prognosis associated specifically with the use of Fuller's Earth or gastric lavage. Nevertheless it is recommended that these measures should still be used and at the earliest opportunity.

28 cases of paraquat poisoning were reported as having been treated by charcoal haemoperfusion, but in each case the treatment was carried out only once and for a limited period of time. Similarly there is no evidence so far that perfusion used in this way improves prognosis.

Evaluation of the effectiveness of an emetic addition to paraquat formulations has so far proved difficult owing to the fact that confirming the involvement of emetic is necessary in each case. Nevertheless it has been possible to show that this addition significantly increases the incidence of early spontaneous vomiting. The study will continue to monitor this aspect of paraquat poisoning. *

Mortality Rate, Course and Therapy of Paraquat Intoxication. T. Zilker, G. Gerber, G. Mathes & V. Clarmann. Toxikologische Abteilung der II, Med. Klinik rechts der Isar der Technischen Universität München, Ismaninger Strasse 22, 8000 München 80, F.R.G.

Twenty-six patients with paraquat intoxication were admitted to our hospital between 1974 and 1981. In five cases, paraquat intoxication was only suspected (two patients suffered skin contamination, two ingested contaminated food and one contaminated soil). All remained asymptomatic and in none was paraquat detected in the urine. Seven cases were the result of accidental ingestion; four survived, and paraquat was detected in the urine of all but one patient. Two patients were murdered and a further 12 cases were the result of attempted suicide. Only one patient in this group survived (mortality rate in suicide + murder cases: 93%, mortality rate in accidental cases: 43–50%).

Those patients with a fatal course can be divided into two groups: 1 Four patients who died acutely within 8–92 hours after ingestion. The cause of death was irreversible shock, metabolic acidosis and circulatory, renal and hepatic failure. 2 Twelve patients who died within 6–15 days as the result of lung fibrosis. One patient died of cerebral oedema after seven days. All patients had acute renal failure and mild liver damage. Whereas the liver recovered in all those cases who survived for more than seven days, renal function did not always recover completely within this time.

The treatment employed included gastric lavage, haemodialysis and haemoperfusion, steroids, bentonite, inhalation of nitrogen, artificial respiration, gut lavage and superoxide dismutase. In summary, only one patient survived suicidal paraquat intoxication. None of the patients (suicidal + accidental) who survived suffered permanent organic damage (liver, kidney or lung).

H-7. EFFICACY OF GUT LAVAGE IN THE REMOVAL OF PARAQUAT IN THE DOG

anesthetized (Vomited with 15 mg)

K Nakamura, MD; M Yamashita, MD; and H Naito, MD
Institute of Clinical Medicine, University of Tsukuba, Sakura-mura,
Niihari-gun, Ibaraki-ken 305, Japan.

A potent emetic has been recently added to the paraquat formulation to reduce the paraquat toxicity by producing strong vomiting after ingestion. Nevertheless, there is no clear evidence that the emetic has reduced the mortality from paraquat since the emetic was added to the paraquat formulation. In our poison control center, the mortality was 90% in the last 11 months. Our collected data show that most patients ingested large doses of paraquat for suicide attempts, which is much more than the smallest fatal dose in man. A question which came up is that enough paraquat for producing toxicity might be still in the gastrointestinal tract even after vomiting when a large dose of paraquat was ingested. It was the purpose of this experiment to estimate how much paraquat would be removed from the intestine using gut lavage in the dog dosed with paraquat either with the emetic or without the emetic.

MATERIALS AND METHODS

Eleven mongrel dogs weighing 10-23 kg were starved for 24 hours before the dogs were anesthetized with 10-15 mg of ketamine hydrochloride/kg body weight intramuscularly. Animals were dosed through a gastric tube with paraquat dichloride either with the emetic or without the emetic after the stomach content was aspirated. The gastric tube was removed immediately after the administration of paraquat. The dogs were kept in a frame. The paraquat dosing solution consisted of the appropriate volume of paraquat diluted with water into a total volume of 50 ml so that animals received 250 mg of paraquat dichloride/kg body weight. The paraquat used in this experiment was a commercial preparation containing 24% paraquat dichloride and 0.05% emetic, PP796, in water. Paraquat with the emetic was given to 5 dogs and paraquat without the emetic to 6 dogs.

The upper duodenum and rectum were ligated 4 hours after paraquat administration under general anesthesia with ketamine, then the gut was lavaged for 20 min using 2,000 ml of warm water through duodenostomy. Lavage fluid was collected through sigmoidostomy to calculate the amount of paraquat in the fluid. Per cent recovery of paraquat from lavaged fluid was expressed by percentage of the amount of paraquat administered.

Table 1. Plasma Concentration of Paraquat (µg/ml)

| Group | 1 hr* | 2 hr* | 4 hr* |
|-------------------------|---------------------|-----------------|-----------------|
| Paraquat+Emetic (n = 5) | 124.5±43.9 NS | 72.9±40.8 NS | 23.7± 6.7 NS |
| Paraquat (n = 6) | 122.7±73.1 | 82.3±41.6 | 52.9±36.2 |
| Mean±SD | NS: Not Significant | | |

Per cent recovery of lavage fluid was also expressed by percentage of 2,000 ml of warm water given through duodenostomy.

Venous blood samples for the measurement of paraquat in plasma were taken 1, 2, and 4 hours after administration. Paraquat in both plasma and lavage fluid were analysed using radioimmunoassay. The difference of mean values between the two groups was tested using Student's t-test.

RESULTS

All dogs vomited within the first 15 min of dosing in the "paraquat with emetic" group, on the other hand, around 1 hour after administration in the "paraquat without emetic" group. Paraquat concentrations in plasma 1 hour after dosing marked the highest levels, then gradually declined (Table 1). Paraquat concentrations in plasma at each sampling point were not significantly different between two groups.

Table 2 shows per cent recoveries of lavage fluid and paraquat from the lavage fluid in both the "paraquat with emetic" group and the "paraquat without emetic" group. Per cent recoveries of both lavage fluid and paraquat from lavage fluid were not significantly different between the two groups.

DISCUSSION

By using our method, we presume that the estimation of the amount of paraquat which is present in the intestine 4 hours after administration is fairly reliable, firstly, because the gut lavage was performed from the upper duodenum through the lower sigmoid. Secondly, as the time consumed for the gut lavage was 20 min, it is unlikely that a significant amount of paraquat was lost from the intestine by absorption during the period of gut lavage. Thirdly, since recoveries of lavage fluid in both groups were 94.5 ± 3.7% and 101.7 ± 12.9%, it is unlikely that a significant amount of the lavage fluid was retained anywhere in the intestine. The procedures of gut lavage in both groups seems identical.

The results of our experiment indicate that the amount of paraquat which was present in the intestine 4 hours after oral administration was only 3-4% of the dose given.

Table 2. Per Cent Recovery of Paraquat and Lavage Fluid

| Group | Lavage Fluid* | Paraquat |
|---------------------------|---------------------|----------|
| Paraquat + Emetic (n = 5) | 94.5± 3.7 | 2.5±1.1 |
| Paraquat (n = 6) | 101.7±12.9 | 4.3±4.1 |
| *Mean±SD | NS: Not Significant | |

[Ipecac 1g]
10-15 mg
20-30 mg

H-7. EFFICACY OF GUT LAVAGE IN THE REMOVAL OF PARAQUAT IN THE DOG

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A potent emetic has been recently added to the paraquat formulation to reduce the paraquat toxicity by producing strong vomiting after ingestion. Nevertheless, there is no clear evidence that the emetic has reduced the mortality from paraquat since the emetic was added to the paraquat formulation. In our poison control center, the mortality was 90% in the last 11 months. Our collected data show that most patients ingested large doses of paraquat for suicide attempts, which is much more than the smallest fatal dose in man. A question which came up is that enough paraquat for producing toxicity might be still in the gastrointestinal tract even after vomiting when a large dose of paraquat was ingested. It was the purpose of this experiment to estimate how much paraquat would be removed from the intestine using gut lavage in the dog dosed with paraquat either with the emetic or without the emetic.

MATERIALS AND METHODS

Eleven mongrel dogs weighing 10-23 kg were starved for 24 hours before the dogs were anesthetized with 10-15 mg of ketamine hydrochloride/kg body weight intramuscularly. Animals were dosed through a gastric tube with paraquat dichloride either with the emetic or without the emetic after the stomach content was aspirated. The gastric tube was removed immediately after the administration of paraquat. The dogs were kept in a frame. The paraquat dosing solution consisted of the appropriate volume of paraquat diluted with water into a total volume of 50 ml so that animals received 250 mg of paraquat dichloride/kg body weight. The paraquat used in this experiment was a commercial preparation containing 24% paraquat dichloride and 0.05% emetic, PP796, in water. Paraquat with the emetic was given to 5 dogs and paraquat without the emetic to 6 dogs.

The upper duodenum and rectum were ligated 4 hours after paraquat administration under general anesthesia with ketamine, then the gut was lavaged for 20 min using 2,000 ml of warm water through duodenostomy. Lavage fluid was collected through sigmoidostomy to calculate the amount of paraquat in the fluid. Per cent recovery of paraquat from lavaged fluid was expressed by percentage of the amount of paraquat administered.

Table 1. Plasma Concentration of Paraquat (µg/ml)

| Group | 1 hr* | 2 hr* | 4 hr* |
|-------------------------|---------------------|-----------|-----------|
| Paraquat+Emetic (n = 5) | 124.5±43.9 | 72.9±40.8 | 23.7± 6.7 |
| | NS | NS | NS |
| Paraquat (n = 6) | 122.7±73.1 | 82.3±41.6 | 52.9±36.2 |
| Mean±SD | NS: Not Significant | | |

Per cent recovery of lavage fluid was also expressed by percentage of 2,000 ml of warm water given through duodenostomy.

Venous blood samples for the measurement of paraquat in plasma were taken 1, 2, and 4 hours after administration. Paraquat in both plasma and lavage fluid were analysed using radioimmunoassay. The difference of mean values between the two groups was tested using Student's t-test.

RESULTS

All dogs vomited within the first 15 min of dosing in the "paraquat with emetic" group, on the other hand, around 1 hour after administration in the "paraquat without emetic" group. Paraquat concentrations in plasma 1 hour after dosing marked the highest levels, then gradually declined (Table 1). Paraquat concentrations in plasma at each sampling point were not significantly different between two groups.

Table 2 shows per cent recoveries of lavage fluid and paraquat from the lavage fluid in both the "paraquat with emetic" group and the "paraquat without emetic" group. Per cent recoveries of both lavage fluid and paraquat from lavage fluid were not significantly different between the two groups.

DISCUSSION

By using our method, we presume that the estimation of the amount of paraquat which is present in the intestine 4 hours after administration is fairly reliable, firstly, because the gut lavage was performed from the upper duodenum through the lower sigmoid. Secondly, as the time consumed for the gut lavage was 20 min, it is unlikely that a significant amount of paraquat was lost from the intestine by absorption during the period of gut lavage. Thirdly, since recoveries of lavage fluid in both groups were 94.5 ± 3.7% and 101.7 ± 12.9%, it is unlikely that a significant amount of the lavage fluid was retained anywhere in the intestine. The procedures of gut lavage in both groups seems identical.

The results of our experiment indicate that the amount of paraquat which was present in the intestine 4 hours after oral administration was only 3-4% of the dose given.

Table 2. Per Cent Recovery of Paraquat and Lavage Fluid

| Group | Lavage Fluid* | Paraquat* |
|---------------------------|---------------------|-----------|
| Paraquat + Emetic (n = 5) | 94.5± 3.7 | 2.5±1.0 |
| Paraquat (n = 6) | 101.7±12.9 | 4.3±4.5 |
| | NS | NS |
| *Mean±SD | NS: Not Significant | |

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Two possibilities seem to explain this finding. First, as most of the paraquat administered might have been absorbed from the intestine soon after administration, the amount which was left in the intestine 4 hours after administration is only fragmental. The highest plasma levels of paraquat were noted 1 hour after administration in our experiment, which might explain this assumption. Second, as a large percentage of paraquat might be still in the stomach even 4 hours after administration, the amount of paraquat which entered into the intestine was only fragmental. Smith and coworkers have shown that between 10% and 40% of orally administered 680 $\mu\text{mol/kg}$ of paraquat was found in the stomach of rats even after 16 hours. Besides, a large dose of paraquat such as the 250 mg/kg used in our experiment is likely to depress gastrointestinal motility and thereby cause delayed entry of paraquat into the intestine.

The results of our experiment also indicate that there is no significant difference between the two groups in per cent recoveries of paraquat which are quite small, 2.5% and 4.3%. Therefore it is questionable that any effects of vomiting could produce any significant effects on these small fractions of administered dose. The efficacy of gut lavage 4 hours after oral ingestion of a large dose of paraquat seems quite questionable since the removal is up to 4% of the total dose given.

In conclusion, when 250 mg/kg of paraquat was given, the emetic did not reduce the amount of paraquat in the intestine compared to the amount after paraquat without the emetic. Plasma concentrations were the same in both groups. Between 3% and 4% of paraquat administered into the stomach was removed using gut lavage 4 hours after administration.

H-8. REDUCTION OF PARAQUAT TOXICITY BY N-ACETYL-L-CYSTEINE

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The in vivo biotransformation of relatively inert compounds to highly cytotoxic intermediates is now recognized as the initial event in the cytotoxicity of a number of common products including paraquat. Highly reactive intermediates may then react with cellular components in a number of ways including peroxidation of lipid membranes. Bus et al (1) recently demonstrated evidence of lipid peroxidation by paraquat in pulmonary tissue.

Paraquat undergoes a single electron reduction to form the reduced radical with microsomal NADPH serving as the source of electrons (2). Reduced paraquat is then reoxidized and the superoxide radical formed. The superoxide radical then dismutates to singlet oxygen which then may peroxidize polyunsaturated membranes to produce lipid hydroperoxides. The spontaneous decomposition of lipid hydroperoxides initiates the chain reaction process of lipid peroxidation. Figure 1 illustrates the mechanism whereby endogenous antioxidants may interrupt the lipid peroxidative chain reactions introduced by paraquat. Superoxide radicals are first converted by superoxide dismutase to ground state molecular oxygen and hydrogen peroxide (3). Hydrogen peroxide is then further detoxified by catalase. Antioxidants such as vitamin E presumably terminate the lipid peroxidative chain

reaction (4). Finally, glutathione peroxidase reduces unstable lipid hydroperoxides to lipid alcohols by oxidizing reduced glutathione thus preventing the formation of lipid free radicals that lead to membrane damage (5).

The clinical use of superoxide dismutase in acute paraquat poisoning has been disappointing in spite of the experimental evidence indicating a protective effect (6). Because superoxide dismutase is a large protein, it does not readily penetrate cell membranes. Further it is rapidly inactivated in vivo. These factors probably explain its lack of therapeutic efficacy. Vitamin E also suppresses superoxide radicals as well

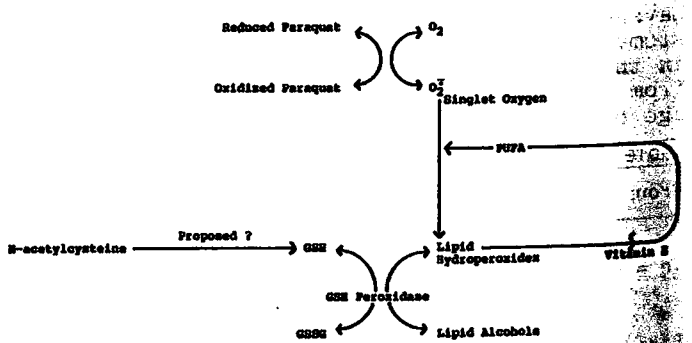


Fig 1 - Adapted from Bus et al (1975).

B-22. THE PLASMA PARAQUAT CONCENTRATION OF DOGS ADMINISTERED PARAQUAT WITH EMETIC

M Yamashita, K Nakamura, S Sato, and H Naito
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High mortality rate has been reported following paraquat ingestion. In order to reduce the mortality rate, emetic has been added to paraquat, but it still accounts for many deaths by paraquat ingestion. Since the opening of our Poison Control Center in September 1981, 20 patients with paraquat poisoning have been admitted to our poison treatment center. Only 2 patients survived and the mortality rate is 90%. The average dose of paraquat ingested by patients treated in our center was 422 mg/kg, which is much higher than LD₅₀, 30 mg/kg in dogs.

There is a possibility that vomiting does not make much difference in blood concentrations when large doses of paraquat are ingested. Studies were carried out to see the blood concentrations following ingestion of paraquat with or without emetics using two kinds of doses.

METHOD

Twenty-six mongrel dogs weighing 10-15 kg were used. Dogs were given nothing by mouth except water on the day of the experiment. Sedation was produced by 10-15 mg/kg of ketamine intramuscularly. Electrocardiogram was monitored and femoral artery and vein were cannulated for monitoring blood gases and blood sampling. The paraquat used in this experiment was commercial preparation containing 24% paraquat and 0.05% emetic or 25% paraquat in water (Figure 1).

A gastric tube was orally inserted and the stomach contents were aspirated. The 30 mg/kg or 250 mg/kg of paraquat with or without emetics diluted with water to make a total volume of 50 ml was injected into the stomach through the gastric tube. The tube was removed immediately after injection of paraquat and dogs were kept in a frame. Blood samples were drawn 1, 2, and 4 hours after paraquat

Table 1. Plasma concentrations following ingestion of paraquat 30 mg/kg (4 determinations per mean \pm standard deviation).

| Hour | Paraquat (g/ml) | Paraquat + Emetic (g/ml) |
|------|-----------------|--------------------------|
| 1 | 5.4 \pm 1.5 | 2.9 \pm 0.8 |
| 2 | 9.2 \pm 1.4 | 3.2 \pm 1.6 |
| 4 | 5.1 \pm 1.2 | 1.3 \pm 0.5 |

administration. Paraquat concentrations in plasma mean values between two groups was tested using student's t-test.

RESULTS

Severe vomiting started about 15 minutes after administration of paraquat with emetics in both 30 mg/kg and 250 mg/kg. Vomiting usually appeared around 1 hour after administration of paraquat with an emetic in 250 mg/kg dose but no vomiting was noted in dogs given 30 mg/kg of paraquat without emetic. One out of the 9 dogs given 250 mg/kg paraquat without emetics vomited within one hour. Supraventricular arrhythmias were noted in dogs given 250 mg/kg of paraquat with emetics. Arterial blood pH, pO₂, and pCO₂ remained within normal limits in all dogs during the experiment. Paraquat concentrations in blood 1, 2, and 4 hours after administration of 30 mg/kg of paraquat into the stomach are shown in Table 1. Values are expressed as mean \pm standard deviations with numbers of determinations in parenthesis. Blood concentrations after paraquat with emetics are significantly lower than that without emetics. However, when large doses (250 mg/kg) of paraquat were given, there are no difference in blood concentrations between paraquat with and without emetic as seen in Table 2.

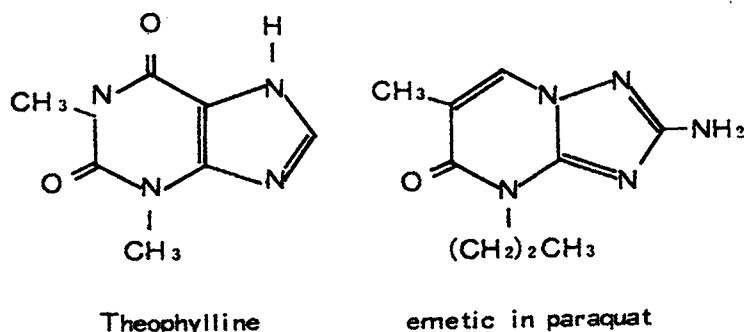


Table 2. Plasma concentrations following ingestion of paraquat 250 mg/kg (9 determinations per mean \pm standard deviation).

| Hour | Paraquat (g/ml) | Paraquat + Emetic (g) |
|------|------------------|-----------------------|
| 1 | 112.4 \pm 42.2 | 106.9 \pm 47.0 |
| 2 | 94.6 \pm 50.2 | 89.6 \pm 39.2 |
| 4 | 53.3 \pm 32.3 | 39.1 \pm 22.9 |

Fig 1 - The structural formulas of theophylline and emetic in paraquat.

4 B-22. THE PLASMA PARAQUAT CONCENTRATION OF DOGS ADMINISTERED PARAQUAT WITH EMETIC

M Yamashita, K Nakamura, S Sato, and H Naito
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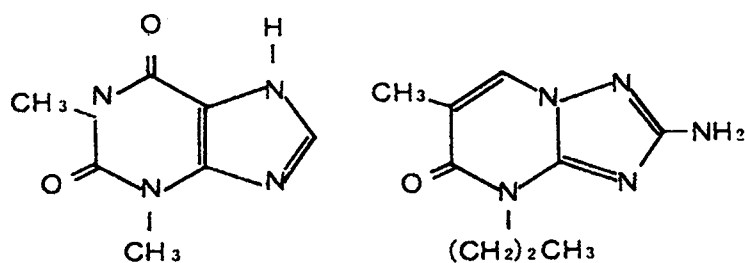


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Table 2. Plasma concentrations following ingestion of paraquat 250 mg/kg (9 determinations per mean \pm standard deviation).

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| 4 | 53.3 \pm 32.3 | 39.1 \pm 22.9 |

DISCUSSION

Since severe vomiting was noted soon after giving paraquat with emetic, quantities of paraquat in the intestine are presumably smaller than that without emetics in both doses. This is reflected in our experiment of 30 mg/kg of paraquat.

However, it is hard to explain that there is no difference in blood concentrations between paraquat with and without emetic when large doses are given. There might be a

possibility that higher doses of emetic in paraquat promote the absorption of paraquat from the intestine. Emetic in paraquat is shown in Figure 1 and is similar in its chemical formula to theophylline. Theophylline is known to increase splanchnic circulation. It is therefore quite likely that a high dose of emetic in paraquat increases splanchnic circulation and thereby intestinal absorption. Supraventricular arrhythmias observed in dogs given 250 mg/kg of paraquat with emetic are also known as a side effect of theophylline.

C. EMERGENCY MEDICAL SERVICE RESPONSE TO TOXICOLOGIC EMERGENCIES

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Each year the American public consumes an estimated 15 billion dollars of health care in almost 5000 emergency departments. Depending on definitions, well over 10% of these visits are for toxicological or pharmacological illnesses. This 1.5 billion in emergency care dollars translates to about 8 million individual instances of human suffering and more annual deaths than those from airplane crashes, bee stings and drownings put together. Providing emergency care 24 hours per day to these patients are 15,000 Emergency Physicians with advice and information from several hundred toxicologists. Regardless of well publicized differences in priorities and techniques, it is shared responsibility to decrease the incidence and severity of all poisoned patients and to use the health care dollars saved for other pressing human needs.

Much has been said and will be said here on treatment modalities. I am not an expert in those fields. You are--and I'm proud to say, many of you are Emergency Physicians. I would like to address pre-hospital care, emergency department care and emphasize prevention--the most effective of all treatment modalities.

Television, magazines and novels all abound with examples of paramedics--those sun-tanned, thin, dextrous machine marvel laden men who see more action in 30 minutes than I see in a week at my emergency department. The concept of taking the hospital to the patient began in this country in the late 1960s and, like anything new in medicine, if some was good, more was better. Some paramedic squads must be staffed by three people just to carry the equipment. No Emergency Medicine is having to face the issue of how much is "Just Right."

All ambulance personnel, regardless of their level of training, should be able to provide some basic services to the poisoned patient. Ipecac should be available on the vehicles and the Emergency Medical Services personnel should be authorized to administer it upon order of a physician. Containers of pills or ingested substances should routinely be found and brought with the patient to the receiving facility. Life support stabilization should be available based on the ambulance personnel's level of training. For Emergency Medical Technicians, this may consist only of Cardio-pulmonary Resuscitation but for paramedics a secure airway and artificial ventilation via an endotracheal tube, intravascular volume expansion and cardiac monitoring may obviate the need for more radical and less effective treatment.

Problem areas exist and help is needed to circumvent or eliminate them. Few jurisdictions will allow EMTs to carry any drug, including Ipecac. Fewer yet will allow them to administer it even on order of a physician. Fears of liability and resistance to change are problems at present not yet overcome. The result is delayed stomach emptying, increased potential for toxicity, and an expensive trip and visit to an emergency department.

Some training programs, including those sponsored by national medical groups, fail to emphasize or mention to the future EMT or paramedic the importance of bringing into the emergency department containers of ingested substances. "Oh, it was Ajax Bowl Cleaner." Valuable information such as "Lemon-Fresh? Spray? Liquid? How much?" goes unanswered. These personnel must be better trained in such simple procedures and that is primarily Emergency

**Prognosis and Treatment of Paraquat Poisoning:
A Review of 28 Cases**

4/6 died with emetic P₈

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Oral intoxications with the bipyridyl herbicide paraquat are always severe. Considering all dilutions, the mortality rate is between 33 and 50% [19]; according to Proudfoot [21] it reaches 78% with the liquid commercial formulation containing 20% paraquat. This mortality rate is probably underestimated, the tendency being to publish treatments resulting in the survival of the patient.

A fatal outcome is likely with as little as one mouthful of the 20% solution, either through circulatory failure within the first 3 d or as a result of progressive and irreversible pulmonary fibrosis in 5 to 31 d [19]. The oxidation of paraquat produces superoxide ions which are responsible for membrane lesions and secondary necrosis of the upper digestive tract, the liver, the renal tubules, and the adrenal glands; and eventually pulmonary fibrosis.

From 1972 through 1981 we observed 28 acute paraquat poisonings. Eleven patients survived. Since a very low dose (as little as 10 mL)

is potentially lethal, it is important to understand why they survived. Were our treatments effective or was the outcome linked to the circumstances of the poisonings?

This paper defines the prognostic factors of paraquat poisoning and analyzes the results of the different treatments. It discusses the cases which survived.

PATIENTS AND METHODS

Twenty-eight acute paraquat poisonings have been reviewed.

The following prognostic factors have been studied: route of administration, sex of the patient, circumstances of the poisoning (accidental/intentional), ingested volume, concentration of the solution, delay between the last meal and the intoxication, lesions of the upper digestive tract (through endoscopic examination since 1977), renal impairment (serum creatinine, urinary creatinine, creatinine clearance, serum and urinary potassium and sodium), pulmonary impairment through chest X-ray, blood gasometry (HbO₂, pH, PaO₂, and since 1973 PaCO₂), lung function tests (vital capacity, functional residual capacity, forced expiratory volume, and since 1979 pulmonary diffusing capacity and lung compliance), and starting in 1974 plasma-paraquat concentrations (first with the colorimetric method [11] and later in 1979 by radio-immunoassay [8]).

From 1974 to 1981 various treatments have been tested: gastric lavage, administration of fuller's earth and induction of diarrhea when patients were hospitalized within the first 24 h after ingestion [23], forced diuresis through furosemide infusion has been tried as well as exchange transfusion in one case [11] and hemodialysis and charcoal hemoperfusion (Gambro-Hemopur). In 1978 and 1979 six patients were given prophylactic artificial ventilation with air mixtures of nitrogen and reduced alveolar oxygen (FIO₂ = 14%). This was performed with the induction of hypothermia to reduce the oxygen need. All other patients were given artificial ventilation only when hypoxia compromised immediate survival.

RESULTS AND DISCUSSION

Prognostic Factors (Table 1)

Route of Administration

Twenty-four out of 28 patients had ingested paraquat; 17 died. Four had inhaled paraquat aerosols and/or suffered skin contaminations; all survived ($p < .05$). Paraquat poisonings through inhalation are always benign because the absorption of the herbicide is very low; most of aerosolized paraquat particles have a diameter of more than 5 μm and

TABLE 1. Paraquat 1972-1981

| Deaths/total | | P (Fisher's test) |
|--|-------|-------------------|
| Per os | 17/24 | <.05 |
| Other routes | 0/4 | |
| Ingestion of paraquat: | | |
| Men | 13/20 | |
| Women | 4/4 | NS |
| Accidental | 5/10 | |
| Intentional | 12/14 | NS |
| One mouthful | 6/12 | |
| >One mouthful | 11/12 | .07 |
| 12% solution | 1/4 | |
| 20% solution | 16/20 | NS |
| Full stomach | 1/5 | |
| Empty stomach | 7/8 | .06 |
| No esophageal lesion | 0/2 | |
| Esophageal lesions | 9/14 | NS |
| No gastric lesion | 0/6 | |
| Gastric lesions | 9/10 | <.01 |
| Organic renal failure | 17/18 | |
| Functional renal failure or no renal failure | 0/6 | <.001 |

cannot reach the alveolar barrier [19]. Percutaneous penetration is a little more effective and a few severe systemic poisonings following skin contamination have been reported [13].

Sex

Paraquat poisoning is much more frequent, but not more severe, in males than in females, because men rather than women work with this herbicide.

Circumstances

Ingestion of paraquat may be intentional or accidental (usually due to the packaging of the herbicide in a household container). The mortality rates in the two groups are not significantly different. This is probably a consequence of the very low minimum lethal dose.

TABLE 2. Ingestion of Paraquat: Moment of Death

| | Delay | Number of cases | Cause of death |
|--------------------|---------|-----------------|---------------------|
| More than one gulp | 12-48 h | 12 deaths | Circulatory failure |
| One gulp or less | 3-31 d | 6 deaths | Pulmonary fibrosis |

Quantity

The minimum lethal dose of paraquat has been estimated to be about 35 mg/kg [19]. A mouthful of the 20% solution amounts to about 55 mg/kg for a 70-kg adult. The same volume of the 12% solution is only 30 mg/kg. Our study does not show any significant difference between the 12% and the 20% groups; however, only four patients ingested the 12% solution. Larger studies might be more conclusive.

The ingestion of one mouthful is associated with a mortality rate of 50%, increasing to 92% ($p = .07$) with more than one mouthful. The course of the poisoning is quite different in these two groups: in the first, 6/12 patients died of extensive pulmonary fibrosis in 5 to 31 d; in the second, 11/12 died of circulatory failure within 48 h (Table 2).

Gastric Content

This could be specified in 13 cases. Five patients had ingested the herbicide shortly after a meal; only one died (of massive intentional poisoning). Eight patients ingested paraquat on an empty stomach; seven died ($p = .06$).

As early as 1971, Matthew [14] pointed out that the course of the intoxication was more severe in patients with an empty stomach. This is a consequence of a well-known characteristic of paraquat: this bipyridyl herbicide is rapidly adsorbed and neutralized once it comes in contact with the soil [4]. This latter property justifies the use of fuller's earth in the treatment of paraquat poisoning. However, the protective effect of gastric repletion could not be demonstrated in experimental animals [16].

Ulcerations of the Upper Digestive Tract

Systematic fiber optic endoscopy was performed on 16 patients between the 3rd hour and the 3rd day of their intoxication. All had buccal ulcerations which were often infected. Deglutition was abolished in five. Only seven of these 16 patients survived. Two had a normal esophagus and did not exhibit any clinical signs other than their buccal ulcerations. Their plasma-paraquat concentrations were very low, so it is likely that they did not swallow the herbicide. Nine out of the 14 patients with esophageal lesions died.

The gastric-endoscopic examination is of greater prognostic value. Nine of 14 patients with gastric (and esophageal) ulcerations died but

six patients without gastric lesions survived ($p < .01$); two also had a normal esophagus (vide supra). The remaining four had ingested the herbicide shortly after a meal. Paraquat was found in their blood, nevertheless plasma concentrations were all below the line separating the fatal cases from survivors according to Proudfoot et al. [21] (vide infra).

Plasma-Paraquat Concentrations

In 1979, Proudfoot and colleagues [21], using blood samples from 79 patients who had ingested paraquat, pointed out the great value of the plasma-paraquat concentration in predicting the outcome of the poisoning. Patients whose plasma-paraquat concentrations do not exceed 2.0, 0.6, 0.3, 0.16, and 0.1 mg/L at 4, 6, 10, 16, and 24 h, respectively, are likely to survive.

In this series, plasma-paraquat concentrations were measured in 17 patients who were admitted before the 30th hour postingestion. Our data (Fig. 1) support the conclusion of Proudfoot et al.: our fatal cases were all above the line and all our survivors were below. The measure of plasma-paraquat concentration is of great value as it predicts the outcome in an early stage of the poisoning.

Renal Failure

Functional renal failure is frequent but has no prognostic value. Digestive fluid losses are often significant and are responsible for the renal function impairment through hypovolemia (Table 1).

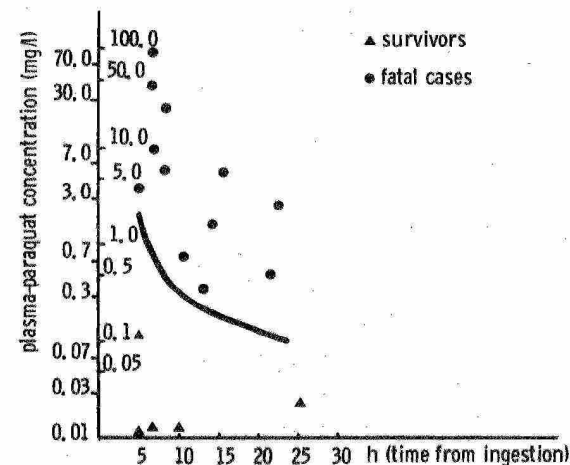


FIG. 1. Plasma-paraquat concentration on admission related to time from ingestion, from 17 patients admitted within 30 h. (Curve according to Proudfoot et al. [21].)

On the contrary, the occurrence of organic renal failure is of great importance in predicting the outcome of the poisoning (Table 1). Only one out of 17 patients with organic renal failure survived (he also had pulmonary impairment which partially resolved). The cause of the renal failure is acute tubular necrosis; it has no specificity. Renal function will return to normal if the patient survives.

Blood gases

These were studied in 11/12 patients who ingested one mouthful or less of paraquat. Those who took more than one mouthful died of circulatory failure within 72 h and, of course, did not show signs of pulmonary fibrosis.

PaO₂. In this study, all patients (6/6) with a PaO₂ under 10.13 kPa (77 torr) died; all others survived. It may be that these high PaO₂ levels were due to the administration of oxygen (certain for three patients and probably for two) before being seen in our unit. It has now been demonstrated that oxygen administration increases the severity of the pulmonary fibrosis [6].

PaCO₂ remained normal longer than PaO₂. It was always above 6.13 kPa (46 torr) when artificial ventilation was started.

Lung Function Tests

These could not be performed daily in most of our patients and it is difficult to appreciate their value as prognostic indicators. Nevertheless, pulmonary diffusing capacity and lung compliance might be of great interest, especially because they decrease earlier than PaO₂ [5, 12].

Treatments (Table 3)

A great number of treatments have been proposed and tested. This shows the anxiety of the toxicologist in this very severe poisoning and the difficulty in finding an effective treatment.

Removal of Paraquat from the Gastrointestinal Tract

In France an emetic has been added to paraquat-containing herbicides and has lowered the toxicity of paraquat by a factor of approximately 5 in monkeys (I.C.I., personal communication). Of six patients who took this new formulation, four died; however, our series may be too small to show a modification of toxicity.

Gastric lavage was performed as soon as possible and up to 6 h after ingestion; forced diarrhea was induced through repeated administration of either cathartics or 10% mannitol and maintained for at least 48 h.

Thirteen patients were given adsorbents. According to Clark [3], activated charcoal is ineffective in adsorbing paraquat. Our patients received a 15% suspension of fuller's earth [23]; only three survived.

TABLE 3. Therapeutic Results

| | Survivals | Deaths | Total |
|------------------------------------|---|----------------------------------|-------|
| Emetic | 2 | 4 | 6 |
| Fuller's earth (normal stomach) | 3 | 10 | 13 |
| Hemodialysis: | | | |
| Hemoperfusion | 1 (for organic renal failure) | 10 (to remove paraquat) | 11 |
| Furosemide | 1 | 17 (anuria:9) (polyuria:8) | 18 |
| Hypoxic breathing mixtures | 1 (normal esophagus plasma paraquat concentration = 0) | 5 | 6 |
| Assisted ventilation | 1 (case above) | 16 | 17 |

None had gastric lesions and all had ingested paraquat shortly after a meal. Thus the efficiency of these treatments is not established. Fuller's earth might be of greater interest if it could be administered earlier (unfortunately fuller's earth is not readily available in France).

Removal of Paraquat from the Blood by Forced Diuresis

Spontaneous urinary paraquat excretion is very important because urinary concentrations are 20 to 50 times greater than plasma concentrations. In patients with maintained diuresis, the renal clearance of paraquat is higher than the clearance of creatinine. This may be explained by glomerular filtration associated with active tubular secretion and nonionic diffusion. Paraquat is not reabsorbed from the renal tubules so that forced diuresis is of no value in removing the herbicide from the blood [18]. Nevertheless, forced diuresis may be helpful because it prevents renal damage by reducing the concentration of paraquat in the renal tubules. In patients without hemodynamic disturbances, forced diuresis is induced with furosemide. A light extracellular dehydration is maintained which improves pulmonary function. In this series 18 patients with developing organic renal failure were given furosemide: nine became anuric but diuresis was maintained in nine. Furosemide infusion did not modify the outcome of these poisonings; 17 out of these 18 patients died.

Elimination of Paraquat by Peritoneal Dialysis, Hemodialysis, or Hemoperfusion over Sorbent Materials

Paraquat has a particular affinity for the lung, and this leads of an accumulation in this organ. High pulmonary concentrations result in fibrosis which is nearly always fatal. Removal of paraquat from the blood would be of value if it could be instituted before toxic levels are achieved in the lung.

Peritoneal dialysis is ineffective [9]. The clearance values of hemodialysis are good at the high plasma-paraquat concentrations which are observed within the first hours of the poisoning. Nevertheless, the amounts removed are very small when compared to those which have been absorbed through the gastrointestinal tract; paraquat has a large volume of distribution, moreover, and plasma concentrations rapidly drop during hemodialysis or hemoperfusion. It should be emphasized that, for low plasma concentrations, clearance values are much higher with hemoperfusion than with hemodialysis and that charcoal hemoperfusion appears to be more effective than resin hemoperfusion [17].

Continuous hemoperfusion was performed by Okonek and colleagues [17] in two patients who had ingested large doses of paraquat and had high plasma concentrations; both survived. There are no similar cases in the literature. We feel that toxic levels are reached in the lung in most cases before hemoperfusion or hemodialysis can be started. Hemoperfusion, however, might be of some interest for patients with borderline plasma concentrations (Fig. 1) [20]. In this series, hemodialysis and hemoperfusion were of no benefit in the 10 cases in which they were used (Table 2).

Gas Regimen in Paraquat Poisoning

Administration of oxygen potentiates paraquat toxicity. An experimental study in mice [22] demonstrated that reduction of oxygen concentration in the ambient air led to a reduction of the mortality rate. Nevertheless, the administration of hypoxic breathing mixtures has not proved to be of any value in human paraquat poisoning. In this series, early administration of mixtures of oxygen and nitrogen was carried out in six patients. It was combined with hypothermia which diminishes the oxygen need. The arterial oxygen tension was maintained at about 6.6 kPa; only one of these patients survived. The absence of ulcerative lesions of his upper digestive tract and a low plasma-paraquat concentration proved that he had ingested only a small amount of the herbicide. No treatment was needed and administration of hypoxic breathing mixtures was stopped the second day of the intoxication. The other five patients had ingested large quantities of paraquat and developed severe poisonings. Hypoxic treatment was undertaken within the first hours but FIO_2 had to be increased daily and finally combined with P.E.E.P. ventilation to maintain PaO_2 . All patients died and in all cases FIO_2 had to be increased above 50%.

Thus hypoxic treatment appears to be of limited value in human

paraquat poisoning. On the other hand, oxygen administration and artificial ventilation should be avoided as long as possible for they may enhance the toxicity of paraquat for the lung. In this series, 17 patients were given artificial ventilation. In six cases it was a prophylactic hypoxic treatment (vide supra) and in 11 cases assisted ventilation was undertaken as late as possible (when spontaneous PaO_2 had dropped under 6.27 kPa). All had a fatal outcome.

Corticosteroids.

Even when these are given in high doses, they do not prevent a fatal outcome [2].

Antidotal Treatments

β -blocking agents block the in vitro and in vivo uptake of paraquat by the lung; in spite of the favorable experimental data, their administration did not prevent fatality [7].

Protection against lipid peroxidation. The main hypothesis to explain paraquat toxicity is that lipid peroxidation is the essential mechanism (Fig. 2). Though α -tocopherol pretreatment proved to reduce mortality in experimental animals, administration of this vitamin after paraquat ingestion did not, so this treatment is of no value in human poisoning [10]. Intravenous infusion of superoxide dismutase and/or glutathione peroxidase has no efficiency because these enzymes do not enter the lung. Their liposomal inclusion might be a solution to this problem [15], and these treatments are being tested in our department.

Survivors

Seven patients who had ingested paraquat survived.

1. Two patients had lesions of the upper digestive tract and low plasma-paraquat concentrations; it is likely that they did not swallow the herbicide.

2. Two patients had esophageal ulcerations but no gastric lesions; in both cases the ingestion of paraquat followed a meal. Both patients had aphagia and had to receive parental nutrition. Nevertheless, their intoxications were not severe and their plasma-paraquat concentration were below the critical line.

3. One patient had buccal and esophageal lesions together with subcardial ulcerations. He had ingested paraquat after a meal. He had no pulmonary dysfunction and his plasma-paraquat concentrations were very low. This man had a hiatus hernia and it is most likely that the cardiac area of the stomach was in the thorax when he took the herbicide.

4. Two patients had lung impairment.

The first patient is also the first case of this series/ he was a 62-year-old farmer, obese, and a heavy smoker. He was admitted on the fourth day of his poisoning with organic renal failure. He had accidentally

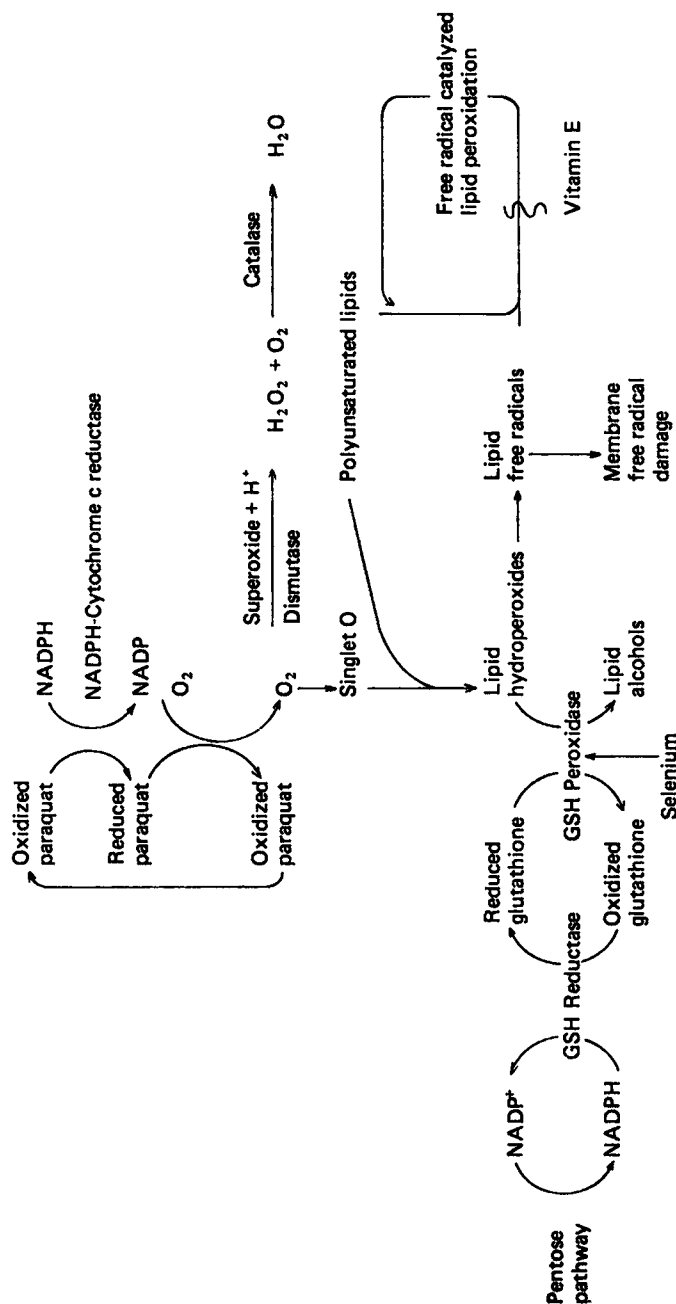


FIG. 2. From Bus et al. [1].

ingested an unknown quantity of paraquat. There is no information on the delay between the accident and his last meal. He had a few buccal erosions but no endoscopic examination was performed. Plasma-paraquat concentration could not be measured. Forced diuresis was induced with furosemide and prevented anuria; nevertheless, hemodialysis had to be performed as a treatment for the renal failure. A renal biopsy was performed on the 10th day following his ingestion and showed pure tubular necrosis. The patient never received oxygen. Chest X-rays were done daily and no change became roentgenographically apparent. However, blood gases and lung function tests showed signs of pulmonary dysfunction. Maximal changes were observed on the 9th day: $PaCO_2$ 6.9 kPa, HbO_2 80%, vital capacity and forced expiratory volume were reduced, pulmonary diffusion capacity was not measured, and the patient refused a pulmonary biopsy. The vital capacity partially improved within 4 years but the forced expiratory volume did not.

The second patient was admitted in 1980, a 13-year-old school boy who had intentionally ingested one mouthful of the herbicide at the end of a meal, 3 d before he entered our unit. He had chemical burns of the mouth and endoscopic examination revealed esophageal ulcerations without gastric lesions. No paraquat was detected in his blood and the urinary paraquat concentration was 40 $\mu\text{g/L}$. He had a functional renal failure which returned to normal after rehydration. Chest X-ray remained unchanged as did blood gases ($PaCO_2 \leq 4.48$ kPa, $PaO_2 \geq 11.5$ kPa). Lung function tests were performed daily and showed a progressive decrease of the pulmonary diffusing capacity which attained 61% of its normal value on the 4th day. Pulmonary compliance remained normal and this patient never received oxygen. The only treatment carried out was parenteral nutrition during 10 d. Five months later the recovery was complete and even the pulmonary diffusion capacity had returned to normal.

In these last two cases a systemic absorption of paraquat is unquestionable. It was sufficient to be responsible for benign pulmonary impairments in both cases and for organic renal failure in one. Nevertheless, the ingested amount was not large enough, in either case, to cause a fatal poisoning.

CONCLUSION

The prognosis of acute paraquat poisoning is strictly linked to the amount of the herbicide absorbed. The plasma concentrations within the first hours of the poisoning directly depend on the amount that has crossed the digestive tract and thus are the best prognostic factor. The outcome of the poisoning is the consequence of its circumstances (ingested amount, full or empty stomach, etc.). The different treatments that have been tested have little or no effect.

SUMMARY

Paraquat poisoning is very severe. When it is ingested, this herbicide may be responsible for causative lesions of the digestive tract, cytolytic hepatitis, renal tubular necrosis, circulatory failure, and/or pulmonary fibrosis. Since a very low dose (as little as one mouthful) is potentially lethal, it is important to understand why 11 of our 28 patients who entered our department for paraquat poisoning survived. The main prognostic factors appear to be the following:

Route of administration. Of four patients who had inhaled paraquat aerosols and/or contaminated their skin with the herbicide, all survived.

Ingested amount. Above 50 mg/kg, patients died of circulatory failure within 72 h; between 35 and 50 mg/kg, a progressive pulmonary fibrosis occurred.

Delay between ingestion and the last meal. Paraquat is adsorbed and neutralized by foodstuffs.

Caustic gastric lesions revealed by early endoscopic examination.

The occurrence of an organic renal failure.

The plasma paraquat concentrations within the first 24 h. Patients whose plasma concentrations do not exceed 2.0, 0.6, 0.3, 0.16, and 0.1 mg/L at 4, 6, 10, 16, and 24 h, respectively, are likely to survive.

The different treatments that have been tested (fuller's earth, forced diarrhea, furosemide, hemodialysis, hemoperfusion, artificial ventilation with hypoxic breathing mixtures) did not modify the initial prognosis.

The 11 survivals are only linked to the circumstances of the poisonings (route of administration, ingested amount, delay between ingestion and the last meal, etc.). The treatments did not modify the outcome.

REFERENCES

- [1] J. S. Bus, S. D. Aust, and J. E. Gibson, Lipid peroxidation: A possible mechanism for paraquat toxicity, *Res. Commun. Chem. Pathol. Pharmacol.*, **11**, 31-38 (1975).
- [2] R. D. Cavalli and K. Fletcher, "An effective treatment for paraquat poisoning," in *Biochemical Mechanism of Paraquat Toxicity* (N. Autor, ed.), Academic, New York, 1977, pp. 213-230.
- [3] D. G. Clark, Inhibition of the absorption of paraquat from the gastrointestinal tract by adsorbents, *Br. J. Ind. Med.*, **28**, 186-188 (1971).
- [4] D. M. Conning, K. Fletcher, and A. A. B. Swann, Paraquat and related bipyridyls, *Br. Med. Bull.*, **25**, 245-249 (1969).
- [5] N. J. Cooke, D. C. Flenley, and H. Matthew, A paraquat poisoning: Serial studies of lung function, *Q. J. Med.*, **42**, 683-692 (1973).

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- [6] J. M. C. Douze and A. N. P. Van Heijst, The paraquat intoxication—Oxygen, a real problem, *Acta Pharmacol. Toxicol.*, **41**, Suppl. 2, 241-245 (1977).
- [7] R. D. Fairshier, N. D. Vaziri, W. P. Smith, F. L. Glauser, and A. F. Wildon, Paraquat poisoning: An analytical toxicologic study of three cases, *Toxicology*, **12**, 259-266 (1979).
- [8] D. Fatori and W. M. Hunter, Radioimmunoassay for serum paraquat, *Clin. Chim. Acta*, **100**, 81-90 (1980).
- [9] H. K. Fischer, M. Humphries, and R. Balls, Paraquat poisoning: Recovery from renal and pulmonary damage, *Ann. Intern. Med.*, **75**, 731-736 (1971).
- [10] K. Fletcher, "Paraquat poisoning," in *Forensic Toxicology* (Proceedings of a symposium held at the Chemical Defense Establishment, Porton Down, June 29-30, 1972) (B. Ballantyne, ed.), Wright, Bristol, England, 1974, pp. 86-98.
- [11] F. Guyon, C. Bismuth, J. P. Leclerc, and F. Cauchy, Intoxication massive par le paraquat mortelle en moins de 24 heures. Données toxicologiques et anatomocliniques, *Eur. J. Toxicol.*, **7**, 182-187 (1974).
- [12] H. F. Lam, J. Takezawa, B. N. Gupta, and E. W. Van Stee, A comparison of the effects of paraquat and diquat on lung compliance, lung volumes, and single breath diffusing capacity in the rat, *Toxicology*, **18**, 111-123 (1980).
- [13] P. J. Levin, L. J. Klaff, A. G. Rose, and A. D. Ferguson, Pulmonary effects of contact exposure to paraquat a clinical and experimental study, *Thorax*, **34**, 150-160 (1979).
- [14] H. Matthew, N. Wright, J. S. Robson, D. Flenley, S. S. Brown, B. E. Heard, E. Housley, A. A. B. Swan, W. P. U. Kennedy, K. W. Donald, G. J. R. McHardy, and L. F. Prescott, Paraquat poisoning: Clinicopathological conference, *Scott. Med. J.*, **16**, 407-421 (1971).
- [15] A. M. Michelson, K. Puget, and P. Durosay, Studies of liposomal superoxide dismutase in rats, *Mol. Physiol.*, **1**, 85-96 (1981).
- [16] R. E. Murray and J. E. Gibson, Lethality and pharmacokinetics of paraquat in rats, *Toxicol. Appl. Pharmacol.*, **19**, 405 (1971).
- [17] S. Okonek, C. A. Baldamus, A. Hofmann, C. J. Schuster, P. B. Bechstein, and B. Zoller, Two survivors of severe paraquat intoxication by "continuous haemoperfusion," *Klin. Wochenschr.*, **57**, 957-959 (1979).
- [18] M. Paillard, Private Communication.
- [19] A. Pasi, *The Toxicology of Paraquat, Diquat and Morfamquat*, Huber, Bern, 1978.
- [20] A. Pottage, A. T. Proudfoot, L. F. Prescott, A. I. Short, and M. J. Stewart, Dialysis for paraquat poisoning, *Scott. Med. J.*, **24**, 256 (1979).
- [21] A. T. Proudfoot, M. S. Stewart, T. Levitt, and B. Widdop, Paraquat poisoning: Significance of plasma-paraquat concentrations, *Lancet*, **2**, 330-332 (1979).

- [22] M. L. Rhodes, D. C. Zavala, and D. Brown, Hypoxic protection in paraquat poisoning, Lab. Invest., 5, 496-500 (1976).
- [23] L. L. Smith, A. Wright, I. Wyatt, and M. S. Rose, Effective treatment for paraquat poisoning in rats and its relevance to the treatment of paraquat poisoning in man, Br. Med. J., 4, 569-571 (1974).

Note added in proof. Lung transplants have been performed unsuccessfully (fibrosis of the transplanted lung) in two cases in the United Kingdom [5]. Recently there was a survival of more than 1 month in the United States (unpublished data).

acute respiratory failure. He had presented 2 or 3 days earlier with dry cough, melæna, hæmatemesis, and bilateral patchy pulmonary infiltrates. He also had hæmolytic anæmia. Lung biopsy showed intra-alveolar hæmorrhage and mild interstitial pulmonary œdema. Clearly inhalation of TMA may have severe systemic effects, including hæmorrhagic pneumonia and hæmolytic anæmia. The cause of the hæmolysis is uncertain but may be immunological. Further studies are necessary to confirm this. Meanwhile occupational exposure to TMA should be borne in mind when patients present with repeated hæmoptysis and hæmolytic anæmia.

We thank Dr Frank Newlands for his assistance in tracing the two patients and obtaining the serum specimens.

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REFERENCES

1. Zeiss CR, Patterson R, Pruzansky JJ, Miller M, Rosenberg M, Levitz D. Trimellitic anhydride induced airway syndromes: clinical and immunologic studies. *J Allergy Clin Immunol* 1977; 60: 96-103.
2. Fawcett IW, Newman-Taylor AJ, Pepys J. Asthma due to inhaled chemical agents—epoxy resin systems containing phthalic anhydride, trimellitic acid anhydride and triethylene tetramine. *Clin Allergy* 1977; 7: 1-14.
3. Chester EH, Schwartz HJ, Payne CB, Greenstein S. Phthalic anhydride asthma. *Clin Allergy* 1977; 7: 15-20.
4. Herbert FA, Orford R. Hemorrhagic pneumonitis due to inhalation of resins containing trimellitic anhydride. *Am Rev Resp Dis* 1978; 117: 241 (abstr).
5. Patterson R, Zeiss C, Roberts M, Pruzansky JJ, Wolkonsky P, Chacon R. Human anti-hapten antibodies in trimellitic anhydride inhalation reactions. *J Clin Invest* 1978; 62: 971-78.

PARAQUAT POISONING: SIGNIFICANCE OF PLASMA-PARAQUAT CONCENTRATIONS

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Summary Plasma-paraquat concentrations were measured in 79 patients who had ingested liquid or granular weedkillers containing paraquat. At any given time after ingestion, the plasma-paraquat concentrations in the patients who died usually exceeded those in the survivors. It is suggested that measurement of plasma-paraquat concentrations is useful in assessing the severity and predicting the outcome of poisoning. Patients whose plasma concentrations do not exceed 2.0, 0.6, 0.3, 0.16, and 0.1 mg/l at 4, 6, 10, 16, and 24 h respectively are likely to survive.

Introduction

PARAQUAT, a herbicide in extensive commercial and domestic use, has gained an unenviable reputation as a potent human poison. Ingestion of the liquid formulation containing 20% paraquat ('Gramoxone', 'Dextro-ne') is associated with a mortality of about 60%,¹⁻⁴ and the minimum lethal dose has been estimated to be as little as 10 ml. The best-known granular preparation, 'Weedol', contains only 2.5% paraquat and 2.5% diquat and is correspondingly less toxic, although any patient

who has ingested the contents of one sachet (about 1.5 g of paraquat) or more is at serious risk (Proudfoot, A. T., unpublished).

Treatment has been directed towards reducing absorption of paraquat by giving large amounts of Fuller's earth or bentonite⁵ orally and by gastric and whole-gut lavage followed by forced diuresis, hæmodialysis, or charcoal hæmoperfusion in attempts to enhance elimination of paraquat before it has caused harm. Assessment of the severity and prognosis of paraquat poisoning and the need to institute active therapy was based, until recently, on the quantity alleged to have been taken and the intensity of the blue colour obtained on testing the urine with alkali/dithionite.⁶ Such arbitrary methods are far from satisfactory and have undoubtedly led to unnecessarily vigorous treatment of some patients and, possibly, failure to treat others who might have benefited. Consequently efforts have been made to measure the concentrations of paraquat in plasma. The gas-liquid-chromatographic method of Draffen et al.⁷ is complex and impracticable in most clinical-chemistry laboratories, but two new methods—one involving radioimmunoassay⁸ and the other colorimetry⁹—can produce a result within an hour and can be used in emergencies. This report describes the prognostic significance of plasma-paraquat concentrations in poisoned patients.

Patients and Methods

79 patients for whom the time of paraquat ingestion was known with reasonable certainty were investigated. 14 were admitted to Guy's Hospital, London, 31 to the Royal Infirmary, Edinburgh, and the remainder came to notice as a result of inquiries to the National Poisons Information Service and the Scottish Poisons Information Bureau. Blood-samples and clinical details of the latter group were obtained by courtesy of the clinicians concerned.

The patients comprised 2 children (aged 3 and 7 years) and 75 adults (29 women and 46 men). 2 men were each admitted twice. The ages of 65 of the adults ranged from 16-81 years (mean 38).

Venous blood-samples (10 ml) were collected into lithium-heparin tubes and the plasma was separated as soon as possible. Plasma-samples which were not analysed immediately were stored at -20°C. In 54 cases only one sample was obtained, but serial samples were taken from the remaining 25 patients. Plasma-paraquat concentrations were measured by gas chromatography in 9 cases, radioimmunoassay in 40 cases, and by the colorimetric method in 30 cases. The three methods give comparable results.^{8,10}

Results

The formulations of paraquat ingested by the patients are listed in the accompanying table. 70 took either promoxone or weedol. 21 of the 27 (78%) who drank promoxone died, whereas only 4 of the 43 (9%) who took weedol died. In 3 fatal cases there was no record of the type of formulation ingested.

71 patients were seen within 35 h of ingestion, and the first plasma-paraquat concentration for each is shown in fig. 1 related semilogarithmically to the time from ingestion and the outcome. In general the plasma concentrations were considerably higher in patients who died than in survivors at the same time after taking the paraquat. However, in the first 5 h this separation was less clear. Patients whose concentrations did not exceed

PARAQUAT FORMULATIONS INGESTED AND NO. OF DEATHS

| Paraquat formulation | | No. of patients | Deaths |
|-------------------------|--------------------------|-----------------|----------|
| Brand name | Paraquat ion content (%) | | |
| Gramoxone ¹ | 20 | 27 | 21 (78%) |
| Gramoxone ² | 20 | 1 | 0 |
| Gramonol ³ | 10 | 1 | 0 |
| Reedol ⁴ | 5 or 2.5 | 43 | 4 (10%) |
| Patheclear ⁵ | 2.5 | 3 | 0 |
| Unknown | .. | 4 | 3 (75%) |

2.0, 0.6, 0.3, 0.16, and 0.1 mg/l at 4, 6, 10, 16, and 24 h after ingestion survived. Plasma-paraquat concentrations were measured in 8 patients admitted more than 15 h after ingestion. In 4 who died the concentrations were 2.8 mg/l at approximately 45 h, 0.39 mg/l at 52 h, 1.15 mg/l at approximately 57 h, and 0.47 mg/l at 104 h. The 4 late admissions who survived had concentrations of 0.015, 0.04, 0.001, and 0.10 mg/l at 68, 72, 115, and 144 h respectively after ingestion.

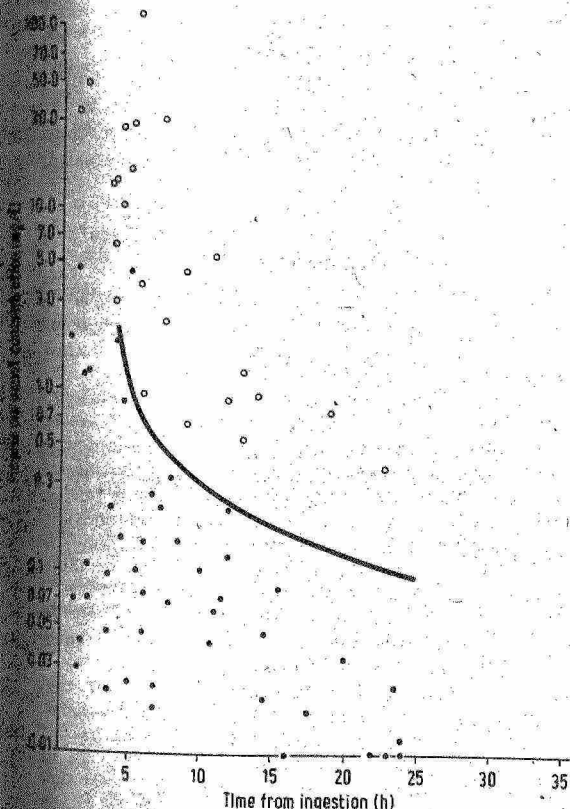


Fig. 1—Plasma-paraquat concentrations on admission related to time from ingestion for 71 patients admitted within 35 h. The line arbitrarily separates fatal cases (open circles) and survivors (closed circles).

Serial plasma-paraquat concentrations were measured in 25 patients (fig. 2), some of whom underwent various forms of treatment in attempts to enhance paraquat elimination. In all but 2 cases, peak plasma-para-

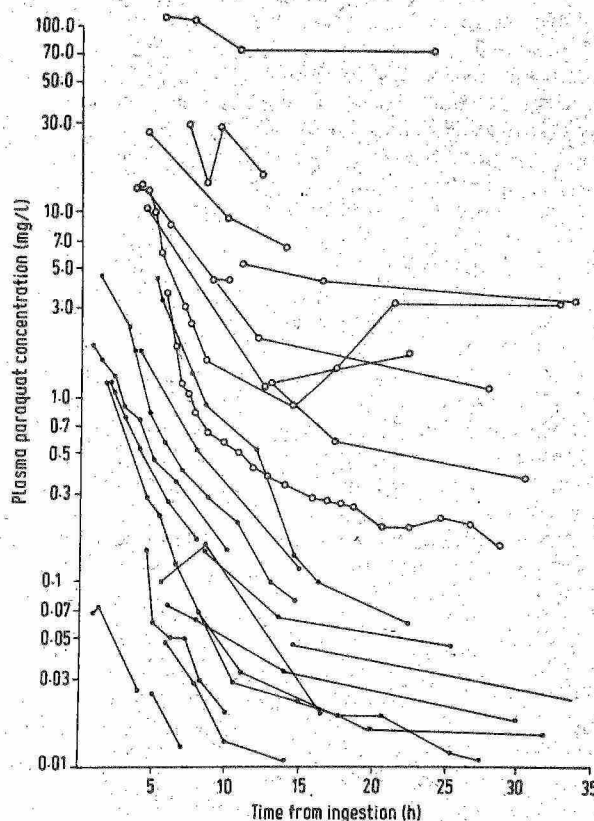


Fig. 2—Serial plasma-paraquat concentrations in 25 patients.

Fatal cases are indicated by open circles and survivors by closed circles.

quat concentrations had been reached before the first blood-samples were drawn, even when the interval between ingestion and sampling was as short as 2 h. Plasma-paraquat concentrations fell rapidly during the first few hours after ingestion, but after 15–20 h they declined more slowly, and in some cases there was little or no fall thereafter.

Discussion

By the time jaundice, renal failure, breathlessness, cyanosis, and radiological changes have made the plight of the patient poisoned with paraquat clinically obvious, it is too late to offer any treatment that might alter the course of events. The alkali/dithionite urine test is useful for confirming paraquat ingestion, but it is of doubtful prognostic value and can be misleading. Wright et al.¹¹ reported that patients who excreted more than 1 mg of paraquat/h 8 h after ingestion died, but decisions about treatment must be made much earlier. With the relatively simple radioimmunoassay and colorimetric techniques plasma-paraquat concentrations can be measured quickly, and it is evident from fig. 1 that at any given time after ingestion the plasma concentrations were usually higher in patients who died than in survivors. Though a line has been drawn in fig. 1 to separate the fatal and non-fatal cases, it is intended only as an approximate guide. The main use of these data should be to protect minimally poisoned patients (as

judged by plasma-paraquat concentrations well below the line) from unnecessary treatment. Similarly, the clinician may decide against treating a patient with a plasma-paraquat concentration well above the line, rather than add to the patient's discomfort by instituting measures which have no hope of success. On the other hand, patients with borderline plasma concentrations should be treated urgently and vigorously in the hope that the balance may be tipped in favour of survival. Further, the careful collection of blood-samples before, during, and after therapy will considerably aid critical evaluation of the efficacy of treatment, for which various claims have been made in the past. The ability to predict the outcome of paraquat poisoning at an early stage would clearly be of great value.

The data in fig. 2 support the contention of Davies et al.¹² that the kinetics of paraquat absorption and elimination in man are similar to those in the dog. Thus paraquat absorption appears to be very rapid (though not necessarily complete), and peak plasma concentrations are attained within 2 h of ingestion. Thereafter, concentrations fall rapidly as the compound is taken up by the tissues and cleared by the kidney. Clearly any technique designed to increase the elimination of absorbed paraquat must be instituted as early as possible, while plasma concentrations are high, if there is to be any hope of removing toxicologically significant quantities. Ideally, plasma-paraquat concentrations should be measured and treatment started at the hospital at which the patient presents. Where this is not practicable, we recommend that the patient be transferred quickly to the nearest specialist treatment centre, after initial preliminary treatment.

We thank the many clinicians and biochemists who took part in this study and, in particular, Dr D. R. Jarvie, Dr R. Illingworth, Dr J. Park, and Dr L. F. Prescott of the Royal Infirmary, Edinburgh, and Mr J. Nunn, Dr P. Crome, and Dr J. A. Vale of the Poisons Unit, Guy's Hospital.

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REFERENCES

1. Malone JDG, Carmody M, Keogh B, O'Dwyer WF. Paracetamol poisoning—a review of nineteen cases. *J Irish Med Ass* 1971; **64**: 59–68.
2. Park J, Proudfoot AT, Prescott LF. Paraquat poisoning—a clinical review of 31 cases. In Fletcher K, ed. *Clinical aspects of paraquat poisoning*. London: I.C.I. Ltd., 1977: 46–54.
3. Fitzgerald GR, Carmody M, Barniville G, O'Dwyer WF, Flanagan M, Silke B. The changing pattern of paraquat poisoning: an epidemiological study. *J Irish Med Ass* 1978; **71**: 103–08.
4. Howard JK. Proceedings of the 8th meeting of European Poisons Control Centres, 1978 (in press).
5. Cavalli RD, Fletcher K. An effective treatment for paraquat poisoning. In Autor, AP, ed. *Biochemical mechanisms of paraquat toxicity*. New York: Academic Press, 1977: 213–30.
6. Berry DJ, Grove J. The determination of paraquat cation in urine. *Clin Chim Acta* 1971; **34**: 5–11.
7. Draffen GH, Clare RA, Davies DL, Murray S, Davies DS. Quantitative determination of the herbicide paraquat in human plasma by gas chromatographic and mass spectrometric methods. *J Chromatogr* 1977; **139**: 311–20.
8. Levitt T. Radioimmunoassay for paraquat. *Lancet* 1977; **ii**: 358.
9. Jarvie DR, Stewart MJ. The rapid extraction of paraquat from plasma using an ion-pair technique. *Clin Chim Acta* 1979; **94**: 241–51.
10. Stewart MJ, Levitt T, Jarvie DR. Emergency estimation of paraquat in plasma. A comparison of the RIA and ion-pair/colorimetric methods. *Clin Chim Acta* 1979; **94**: 253–57.
11. Wright N, Yeoman WB, Hale KA. Assessment of severity of paraquat poisoning. *Br Med J* 1978; **ii**: 396.
12. Davies DS, Hawksworth GM, Bennett PN. Paraquat poisoning. In Duncan WAM, ed. *Clinical toxicology, proceedings of European Society of Toxicology*. Amsterdam: Excerpta Medica, 1977; vol xviii, 21–26.

Preliminary Communication

ACROMEGALY AND NARCOLEPSY

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Summary 7 of 372 acromegalic patients had troublesome episodes of paroxysmal daytime sleep. Although 3 patients had complete resolution of symptoms within a few days of pituitary surgery, the cause of this increased frequency of narcolepsy among acromegalic patients is not known.

INTRODUCTION

OVER the past two decades we have been aware of an increase in the number of acromegalic patients complaining of paroxysmal daytime sleep which occurs regularly at times not normally conducive to sleep. Because narcolepsy is not a recognised complication of acromegaly, we report details of 7 acromegalic patients with this condition.

PATIENTS

7 of the 372 acromegalic patients for whom we have kept records came to our attention because they had had troublesome episodes of daytime sleep (see table). None of 192 patients with other pituitary disorders attending our clinic during the same period had similar episodes of daytime somnolence.

Narcolepsy is difficult to distinguish from hypersomnia. Narcoleptic attacks are characteristically paroxysmal and, while often encountered in situations not conducive to sleep, may occur under other, more unusual circumstances which stamp them as clearly abnormal. From our series several acromegalic patients with more continuous drowsiness, attributable, for example, to lack of nocturnal sleep (due to carpal-tunnel syndrome), urinary frequency related to diabetes, to treatment with methyldopa, to hypothyroidism or adrenal insufficiency associated but unrelated cerebrovascular disease. In addition, we also excluded patients in whom daytime sleep occurred after meals, on public transport, while watching television, when reclining in a chair, or from work; we found it difficult to distinguish between these circumstances and what might be found, on occasion, in narcolepsy. The sleep disturbance in our cases was severe, and an embarrassment to the patients.

DISCUSSION

None of our patients experienced other members of the narcoleptic tetrad (cataplexy, sleep paralysis, hypnagogic hallucinations). Nevertheless, we consider their episodic hypersomnia is properly called narcolepsy. Only 15% of narcoleptic patients have all members of the tetrad.¹ In a series of 400 patients

Bobro
BSPo

Paraquat 100mg/kg -- after one hour -- test chemicals 1,000 mg/kg

| Test Chemicals | No of Test Animal | No of Survived Animal | | |
|--|-------------------------|-----------------------|--------|--------|
| | | 7days | 10days | 14days |
| paraquat only | 8 | 1 | 1 | 1 |
| lignosulphonate | 8 | 6 | 6 | 6 |
| β -naphthalene sulphonate formalin | 8 | 8 | 8 | 8 |
| tannic acid | 8 | 6 | 6 | 6 |

Paraquat 200mg/kg -- after one hour -- test chemicals 1,000mg/kg

| Test Chemicals | No of Test Animal | No of Survived Animal | | |
|--|-------------------------|-----------------------|--------|--------|
| | | 7days | 10days | 14days |
| paraquat only | 8 | 1 | 1 | 1 |
| lignosulphonate | 8 | 1 | 1 | 1 |
| β -naphthalene sulphonate formalin | 8 | 5 | 5 | 5 |

Paraquat 200mg/kg -- after one hour -- tungstophosphoric acid (PWA)

| Test Chemicals | Dose mg/kg | No of Test Animal | No of Survived Animal | | | | |
|----------------|---------------|-------------------------|-----------------------|---|---|---|--------|
| | | | 1 | 3 | 5 | 7 | 10days |
| paraquat only | --- | 10 | 9 | 4 | 2 | 1 | 1 |
| PWA | 250 | 10 | 9 | 8 | 1 | 1 | 1 |
| " | 500 | 10 | 10 | 8 | 6 | 6 | 6 |
| " | 1000 | 10 | 8 | 6 | 4 | 4 | 4 |

D. Emetic Activity of PP-796

Emetic Activity in Dogs

| dose mg/kg | dose by man* ml/50kg | caused vomiting after |
|---------------|-------------------------|--------------------------------------|
| 0.1 | 10 | (no effect within 30 minutes) |
| 0.2 | 20 | 10 minutes |
| 0.4 | 40 | (almost no effect within 30 minutes) |
| 2.0 | 200 | 5 minutes |

* volume calculated assuming that Gramoxone contains 0.05% PP-796

Emetic Activity in Frogs

| test chemicals | dose mg/kg | vomitted animals/test animals |
|---|---------------|-------------------------------|
| PP-796 | 100 | 1/5 |
| $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ | 100 | 3/5 |
| ipecac powder | 100 | 0/5 |
| tartaric acid antimol K | 100 | 0/5 |

PP-796 Added to Gramoxone: Effects on Acute Toxicity in Rats

Biological Research Laboratory,
Research & Development Dept.,
Nihon Nohyaku Co., Ltd

It is reported that PP-796 achieved some effects in delaying absorption of paraquat from the digestive organs in studies using rats, though it is impossible to examine the emetic action of PP-796 using rats. In this study, the effects of PP-796 on acute toxicity by Gramoxone were investigated using rats.

1. Materials and Methods

1) Test Formulations

Gramoxone manufactured by Nihon Nohyaku

Gramoxone containing PP-796 by 0.05% W/W manufactured by
Teijin Agrochemicals

(components of Gramoxone): 1,1'-dimethyl-4,4'-bipyridinium

dichloride 24.0%

water and others 76.0%

2) Test Animals

SD male rats (body weight: 120-150 g)

3) Testing Methods

Diluted Gramoxone with distilled water to obtain test formulations containing 2% paraquat. The formulations were administered according to the prescribed dose by an oral route by a stomach probe. The food was removed from 18:00 of the day before administration and started feeding one hour after administration.

2. Results

The test results are summarised in Table 1.

Table 1. Number of Survived Rats and Percentage of Survival

| | dose (mg/kg) | number of rats | Number of survived rats | | | | | | | | | survival (%) |
|--------------------|-----------------|-------------------|-------------------------|----|---|---|---|---|---|---|--------|-----------------|
| | | | 1d | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 days | |
| Gramoxone | 35 | 5 | 5 | 4 | 4 | 4 | 3 | 3 | 3 | 3 | 3 | 60 |
| | 46 | 5 | 5 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 80 |
| | 59 | 10 | 10 | 10 | 8 | 5 | 5 | 4 | 4 | 3 | 3 | 30 |
| | 77 | 10 | 10 | 8 | 4 | 4 | 2 | 1 | 0 | 0 | 0 | 0 |
| | 100 | 10 | 6 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 130 | 10 | 3 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 169 | 10 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 220 | 10 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 286 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 35 | 5 | 5 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 80 |
| Gramoxone + PP-796 | 46 | 5 | 5 | 4 | 4 | 4 | 4 | 3 | 3 | 3 | 3 | 60 |
| | 59 | 10 | 10 | 9 | 5 | 4 | 3 | 3 | 3 | 3 | 3 | 30 |
| | 77 | 10 | 10 | 7 | 6 | 4 | 3 | 2 | 2 | 2 | 2 | 20 |
| | 100 | 10 | 5 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 130 | 10 | 5 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 169 | 10 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 220 | 10 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 286 | 10 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 35 | 5 | 5 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 80 |
| | 46 | 5 | 5 | 4 | 4 | 4 | 4 | 3 | 3 | 3 | 3 | 60 |

3. Conclusion

As can be seen from the results of this study using rats which lack the vomiting centres, PP-796 showed little effect for reducing acute toxicity caused by Gramoxone or to save rats from death.

We consider further studies are essential in dogs or monkeys having the vomiting centres to evaluate the effectiveness of PP-796.

Effects of Gramoxone containing PP-796 on Users

Biological Research Laboratory, R & D Dept, Nihon Nohyaku

PP-796 is added to Gramoxone to induce vomiting when the pesticide is swallowed. We have surveyed as to nausea, vomiting and other possible effects of diluted Gramoxone on users by setting out questionnaires.

1. Materials and Methods

1) Test Formulations

Gramoxone on the market prepared by Nihon Nohyaku

Gramoxone containing PP-796 by 0.05% W/W prepared by Teijin Agrochemicals

(components: 1,1'-dimethyl-4,4'-bipyridinium dichloride ... 24.0%

water and others 76.0%)

2) Volunteers

18 males (age: 26-47), staff of this laboratory

3) Testing Method

Gramoxone on the market and Gramoxone containing PP-796 were diluted respectively with 150 ml surfactant (Kusarino) and 50 l water. The test formulations were applied to a test field (5 a) by power sprayers for about 10 - 20 minutes. The volunteers were exposed to the spray mist in the field, then filled out the questionnaires. The test formulations were masked to make them hard to be discriminated, thus enabling us to obtain unprejudiced comments.

2. Results

Answers of the volunteers to the questionnaires are summarised in

Table 1.

Table 1. Effects of Gramoxone containing PP-796 on Users

| Questions | Gramoxone | | Gramoxone+PP-796 | |
|---------------------------------------|-----------|----|------------------|----|
| | Yes | No | Yes | No |
| Have you a headache? | 0 | 18 | 0 | 13 |
| Are your eyes misted with tears? | 0 | 18 | 0 | 18 |
| Are your eyes irritated? | 0 | 18 | 0 | 18 |
| Have you a pain in your eyes? | 0 | 18 | 0 | 18 |
| Do you feel sick? | 1 | 17 | 0 | 18 |
| Do you feel like vomiting? | 0 | 18 | 0 | 18 |
| Does your skin smart? | 0 | 18 | 0 | 18 |
| Have you a tingling pain in the skin? | 0 | 18 | 0 | 18 |
| Is your skin feverish? | 0 | 18 | 1 | 17 |
| Have you a sore throat? | 0 | 18 | 0 | 18 |
| Have you a sore tongue? | 0 | 18 | 0 | 18 |

As can be seen from Table 1, Gramoxone containing PP-796 differs little from Gramoxone in the effects on users. Only two of the volunteers exposed to Gramoxone and Gramoxone containing PP-796 answered "yes". Before tests, we thought Gramoxone containing PP-796 might cause nausea or vomiting, but no one exposed to the spray mist of the formulation had such a trouble. Three persons had a very slight irritation in the noses on inhaling Gramoxone containing PP-796, but the effect disappeared soon.

3. Conclusion

The spray mist of Gramoxone containing PP-796 caused no adverse effects such as vomiting and irritation on users like Gramoxone on the market. Gramoxone mixing the emetic shows the emetic action when swallowed, but in this study it has been proved that it loses the action when diluted. So, we have concluded that the formulation has no adverse effects on users.

Questionnaires on Application of Gramoxone

- effects of Gramoxone containing PP-796 or Capsicum Tincture on Users -

Biological Research Laboratory, R & D Dept

Nihon Nohyaku Co Ltd

A proposal to add an emetic or alarming agent to Gramoxone has been made as a measure to reduce the risk of accidental swallowing or drinking of Gramoxone. We have prepared two test formulations of Gramoxone containing an emetic (PP-796) and Gramoxone containing capsicum tincture and studied the effects on man of the spray mist of the formulations by setting out questionnaires.

1. Materials and Methods

1) Test formulations

Gramoxone on the market manufactured by Nihon Nohyaku

Gramoxone containing PP-796 by 0.05% W/W manufactured by Teijin Agrochemical

Gramoxone containing capsicum tincture (Japanese Pharmacopoeia; Hoei Yakko)

2) Volunteers

18 males (age; 26 - 47), staff of this laboratory

3) Testing method

Diluted Gramoxone on the market, Gramoxone containing PP-796 and

Gramoxone containing capsicum tincture with 150 ml surfactant

(Kusarino) and 50 l water. Sprayed test formulations over a test

field (5a) by power sprayers for about 10 - 20 minutes. The

volunteers in the test field were exposed to the spray mist, then

filled out the questionnaires. The test formulations were masked

to make them hard to be discriminated, thus enabling us to obtain

unprejudiced comments. The volume of capsicum tincture to be added

to Gramoxone was determined by the following method; the volunteers

tasted aqueous solutions containing 0.3, 1, 3 & 10% of capsicum

tincture, and on the basis of their comments, adopted the concentrations which all felt pungent or very pungent.

2. Results

The following table shows the results of the pungency sensory test made to determine the volume of capsicum tincture to be added to Gramoxone.

Table 1. Capsicum Tincture Pungency Sensory Test

| volunteers | concentrations of capsicum tincture | | | |
|------------|-------------------------------------|----|----|------|
| | 0.3% | 1% | 3% | 10%* |
| A | Δ | o | o | ⊙ |
| B | x | Δ | o | ⊙ |
| C | x | o | o | ⊙ |
| D | Δ | o | o | ⊙ |
| E | Δ | o | ⊙ | ⊙ |
| F | Δ | o | ⊙ | ⊙ |
| G | o | ⊙ | ⊙ | ⊙ |
| H | Δ | Δ | o | ⊙ |
| I | x | o | ⊙ | ⊙ |
| J | Δ | Δ | o | ⊙ |
| K | Δ | Δ | o | ⊙ |
| L | Δ | o | ⊙ | ⊙ |
| M | x | x | o | o |

* diluted with water

x: not pungent, Δ:slightly pungent, o:pungent, ⊙:very pungent,
⊙: extremely pungnet

All the volunteers felt the solution containing over 3% capsicum tincture pungent. The solution containing 10% capsicum tincture was quite pungent to all except one. On the basis of the results,

we have determined to add 3% capsicum tincture to Gramoxone. Table 2 shows the comments from the volunteers exposed to Gramoxone, Gramoxone containing the emetic and Gramoxone containing capsicum tincture.

Table 2. Effects of Gramoxone, Gramoxone containing PP-796 and Gramoxone containing Capsicum Tincture

| Questions | Gramoxone | | Gramoxone + PP-796 | | Gramoxone + Capsicum Tinctur | |
|---------------------------------------|-----------|----|--------------------|----|------------------------------|----|
| | Yes | No | Yes | No | Yes | No |
| Have you a headache? | 0 | 18 | 0 | 18 | 0 | 18 |
| Are your eyes misted with tears? | 0 | 18 | 0 | 18 | 0 | 18 |
| Are your eyes irritated? | 0 | 18 | 0 | 18 | 0 | 18 |
| Have you a pain in your eyes? | 0 | 18 | 0 | 18 | 0 | 18 |
| Do you feel sick? | 1 | 17 | 0 | 18 | 0 | 18 |
| Do you feel like vomiting? | 0 | 18 | 0 | 18 | 0 | 18 |
| Does your skin smart? | 0 | 18 | 0 | 18 | 0 | 18 |
| Have you a tingling pain in the skin? | 0 | 18 | 0 | 18 | 0 | 18 |
| Is your skin feverish? | 0 | 18 | 1 | 17 | 0 | 18 |
| Have you a sore throat? | 0 | 18 | 0 | 18 | 0 | 18 |
| Have you a sore tongue? | 0 | 18 | 0 | 18 | 0 | 18 |

As can be seen from Table 2, Gramoxone and Gramoxone containing PP-796 gave some effects on one volunteer each, while Gramoxone containing capsicum tincture didn't. None felt sick or like vomiting following exposure to Gramoxone containing the emetic. None had a sore throat or tongue after exposure to Gramoxone containing capsicum tincture. Three volunteers had a very slight irritation in their noses on inhalation of the formulation mixing PP-796, but the effect disappeared soon.

3. Conclusion

The spray mist of Gramoxone formulation mixing PP-796 caused neither nausea nor irritation in those who exposed to the mist like Gramoxone on the market. The formulation mixing the emetic shows the emetic action when swallowed, but in this study it has been proved that it loses the action if diluted. Thus, we have concluded that the formulation has no adverse effects on users.

Gramoxone mixing capsicum tincture gave no irritation to those who exposed to the spray mist of the formulation, so it has no adverse effects on users. The pungent taste of the diluted solution of capsicum tincture is familiar to us, so it is unlikely that we are alarmed at drinking Gramoxone with capsicum tincture by unexperienced taste. However, capsicum tincture may contribute to make Gramoxone hard to drink and to reduce the risk of accidental drinking.

Screening Test for Distasteful Agents to be added to Gramoxone

1. Purpose of Study

Screening test for distasteful agents was conducted to study efficacy of Gramoxone mixing distasteful agents in reducing accidental drinking and suicide. Sensory test was also made for Gramoxone mixing an emetic or purgative.

2. Testing Method

1) Sensory test

Test chemicals were diluted with prescribed amount of distilled water for taste test by volunteers. On the basis of the comments from the volunteers, the marking of test solutions with -, +, ++ and +++ was made according to the extent of bitterness and pungency. The tastes of a purgative and emetic were expressed in words.

2) Observation of change on standing of Gramoxone/distasteful agent admixtures

Prepared test solutions by mixing Gramoxone and solutions of test chemicals so as to make the test solutions contain 20% Gramoxone and 1, 2 & 3% each of distasteful agents. Observed precipitates after leaving the solutions for 3 weeks at ordinary temperature. The concentration of an emetic (PP-796) was 0.5%.

3. Results

In sensory test six distasteful agents were evaluated as to bitterness/astringency and pungency. Of the test chemicals, Japanese green gentian powder and capsicum tincture found to have the strongest

bitter taste and pungent taste, respectively. Japanese green gentian powder is very expensive (¥30,000/kg) and it requires extraction with hot water, so it was evaluated as not available for practical use. In contrast, capsicum tincture makes Gramoxone strongly pungent and costs only ¥1,560/kg, so it was evaluated as practicable. However, we consider it necessary to know how much capsicum tincture the makers can supply. As to a purgative and emetic, they had no strong disgusting tastes.

4. Prescription for Gramoxone plus Capsicum Tincture Formulation

| | |
|---|--------|
| Gramoxone (purity: 25.0%) | 964 ml |
| capsicum tincture (specific gravity:0.83) | 36 ml |
| Gramoxone content | 24.3% |

The addition of 3% W/W or 3.6% V/V of capsicum tincture to Gramoxone by which Gramoxone has disgusting taste enables modification of prescription without changing the indication of active ingredient on the present labels.

Screening Test for Distasteful Agents to be added to Gramoxone

| | agents | test chemicals | concentrations | | | | solubility in water (g/100ml) | price (¥/kg) | precipitates |
|--------------------|------------|---------------------------------------|-----------------|-----------|------------------------|------------------------|-------------------------------|--------------|--------------|
| | | | 0.5% | 1% | 2% | 3% | | | |
| distasteful agents | bitterness | MgCl ₂ · 6H ₂ O | - | - | - | + | 281/0°C | 40 | - |
| | | tannic acid powder* | - | - | + | + | | 1,000 | + |
| | | gential powder | + | + | ++ | +++ | | 30,000 | - |
| | | 'Nigaki' powder** | - | - | + | + | | 1,700 | - |
| | | Tabasco | - | - | + | + | | 4,400 | - |
| | | capsicum tincture*** | + | + | + | ++ | | 1,560 | - |
| purgative | emetics | MgSO ₄ · 7H ₂ O | | tasteless | tasteless | slightly bitter | 120/20°C | 35 | - |
| | | CuSO ₄ · 5H ₂ O | | tasteless | slightly sweet & rough | slightly sweet & rough | 24.3/0°C | 200 | + |
| | | ZnSO ₄ · 7H ₂ O | | tasteless | tasteless | tasteless | 115/0°C | 100 | - |
| | | tartar emetic | | tasteless | tasteless | tasteless | 5.3/8.7°C | 1,500 | - |
| | | ipecaac powder | | tasteless | slightly bitter | slightly bitter | | 12,500 | - |
| | | PP-796 | slightly bitter | | | | 0.5/room temp | | - |
| | | | | | | | | | |

* evaluated by bitterness and astringency

** 'Nigaki' : Picrasma quassioides

*** distributors: Ebisu Yakuhin & Maruishi Seiyaku (makers are not known)

5. Conclusion

On the basis of findings of this study, we recommend capsicum tincture as an additive for Gramoxone from the viewpoints of its efficacy in making Gramoxone distasteful and its price. Recommendable concentration of capsicum tincture is 3% W/W. Meanwhile, we are surveying the capacity of supply of capsicum tincture makers.

6. Further Studies

- 1) Development of 'hard-to-drink' formulations of Gramoxone (eg: Gramoxone in the sol)
- 2) Evaluation of a change on standing of the pungent taste of capsicum tincture

Questionnaires on Gramoxone Poisoning of Yamanashi Farmers

Interviewee: Mr Kosugi, Plant Protection Dept, Yamanashi Prefectural Office

Interviewed on 5 Sept 1978 by Yumoto

Some poisoning accidents in application of Gramoxone were reported in Yamanashi Prefecture in the 1977 agrochemical year. To cope with the situation, Yamanashi Prefectural Office has carried out investigation through the staff responsible for giving guidance as to pest control. (Mr Kosugi estimates poisoning accidents in application of Gramoxone account for 20-30% of all cases of application.)

Questionnaires were set out to 650 farmers and about 300 farmers answered. The number of farmers affected by Gramoxone was below the expectations; of the answerers, only 4 had some abnormal symptoms requiring further survey. The Prefectural Office considers that it is not necessary to lay down stricter regulations on the use of Gramoxone. However, as a measure to reduce poisoning accidents, the Prefectural Office is planning to give guidance for a more suitable spraying method by the 'Sunfonote' sprayer.

Note: 'Parazet' & 'Nakusu' -- Herbicides similar to Gramoxone

It is difficult for Yamanashi Prefectural Office to regulate the use of these herbicides because they are registered as herbicides for non-agricultural area use. However, in actual they are applied to agricultural areas, so the Prefectural Office is to ask the Ministry of Agriculture, Forestry and Fisheries to give proper guidance for the use of these herbicides.

Survey of Four Farmers affected by Gramoxone

(1) Answers of Four Farmers

Case 1. male, 43-year-old

Used Gramoxone for over 5 years for controlling weeds in the peach garden and mulberry field. Sprayed Gramoxone with rubber gloves on. Developed a stomachache after application. Consumption, 300cc bottle x 20 a year.

Case 2. male, 35-year-old

Used Gramoxone for over 5 years for the mulberry field and non-agricultural areas. Sprayed Gramoxone wearing a dust mask and covering himself with a towel. Suffered from a headache and languor following application. Consumption, 100cc bottle x 15 a year.

Case 3. male, 47-year-old

Used Gramoxone for over 5 years for the mulberry field and farmyard. Sprayed Gramoxone with no special protective wears on. Complaint, lack of appetite. Consumption, 300cc bottle x 3 a year.

Case 4. male, 46-year-old

Used Gramoxone for over 5 years Sprayed Gramoxone wearing a dust mask, rubber gloves and protective trousers and covering himself with a towel. Suffered from languor, perspiration and diarrhoea. Consumption, 300cc bottle x 30 a year.

(2) Interviews with the Four Farmers

Case 1. Type of field/Area: mulberry field (4 tan, or about 1 acre) and part of peach garden

Time of Applctn: A break in the rainy season (beginning of June),
10:00 - 12:00 am

Dilution: Diluted two 300cc bottles with 300 l water

Sprayed by: A power sprayer

Period: 3 consecutive days, twice in June

Abnormal Symptoms: Developed for the first time a slight stomachache at the latest application time in June.

Cause of Abnormality: The heat and overwork made the farmer easy to be affected by Gramoxone. He didn't see a doctor or keep quiet and continued to work because the stomachache was not a violent one.

Measure for Safe Use: The farmer will take care of himself to avert Gramoxone poisoning.

Case 2. Type of field/Area: Mulberry field (80a)

Time of Applctn: late April and mid-May (before the rainy season)

Dilution: Diluted two 100cc bottles with 300 l water

Sprayed by: A power sprayer

Period: 2 consecutive days (3 hours a day), twice

Abnormal Symptoms: Had a slight headache and a hatred for the sprayed mist of Gramoxone, but developed no significant effects causing discontinuation of his work.

Cause of Abnormalities: The heat and insufficient protection against the sprayed mist.

Measure for Safe Use: He is to apply the herbicide in hours except for the hottest part of the day and also put on protective wears.

Case 3. Type of field/Area: Mulberry field (20a)

Time of Applctn: A hot summer day (except the hottest hours)

Dilution: Diluted 1/10 of the content of a 300cc bottle with 20 l water

Sprayed by: An automatic pressure sprayer

Period: 3 hours each in the morning and afternoon

Abnormal Symptoms: The farmer formerly felt sick when he prepared the diluted formulation neglecting the handling precautions and without wearing gloves. After that he occasionally felt sick in handling Gramoxone at the memory of the shock of the first poisoning accident. This year, he used Gramoxone giving due regard to the precautions on the label so he had only a slight sickness after smelling the herbicide in the time of application.

Measure for Safe Use: Considering the risk of poisoning arising from carelessness in handling, he is to be more attentive in application of Gramoxone. He has given advice to his friends to handle Gramoxone according to precautions.

Case 4. Type of field/Area: Orchard (2 ha)

Time of Applctn: A fine interval of the rainy season, in the full heat of the day

Dilution: Diluted 300cc bottle with 200 l water and sprayed the volume per 10a of the orchard

Sprayed by: "SS Pest Controlling Machine"

Period: 3 consecutive days (for 3-4 hours in the hottest part of the day) The farmer applied Gramoxone in the interval of peach tree pest control and washed well the sprayer before and after use. He felt his work schedule too tight, but continued to work because it was the busiest farming season.

Abnormal Symptoms: He felt a little exhausted because of the

tight work schedule. He disliked the smell of Gramoxone, but he has to use the herbicide to achieve an effective weed control.

Measure for Safe Use: He will take care of his health to avert the risk of poisoning. He will make a safe and reasonable work schedule and will spray Gramoxone in hours except the hottest part of the day.

| compounds | dose (mg/kg) | survived animals | | pharmacological action to be expected |
|----------------------------------|-------------------|------------------|-------------------|--|
| | | with antidote | paraquat only | |
| N,N-Diphenyl-p-phenylene diamine | 500 po | 2/9 | 5/9 ^b | SH-antioxidant |
| " | 500 po | 1/9 | 6/9 ^b | |
| Dimercaptopropanol | 20 x 2 ip | 4/8 | 7/8 ^c | SH-antioxidant |
| Penicillamine | 200x3 po | 1/8 | 1/8 ^d | SH-antioxidant |
| Glucuronic acid | 100 ip | 6/9 | 6/9 ^b | general antidote |
| Thyroxine | 20 x 2 ip | 2/8 | 7/8 ^c | depression of O ₂ concentration in the tissue |
| α-BHC | 50 po | 5/8 | 7/8 ^c | inducer of drug metabolizing enzyme |
| Cortisone | 20 x 2 po | 6/8 | 7/8 ^c | anti-inflammatory |
| " | 20 x 3 ip | 1/8 | 3/10 ^c | |
| Predonisolone | 10 x 2 po | 7/8 | 7/8 ^c | anti-inflammatory |
| " | 10 x 4 po | 2/8 | 1/8 ^d | |
| Dexamethasone | 5 x 2 ip | 0/8 | 3/10 ^c | anti-inflammatory |
| Ethylnitrosourea | 20 ip | 1/8 | 3/8 ^c | immuno-suppression |
| PAM | 62.5x3ip | 1/8 | 2/8 ^c | competition from similarity of chemical structure |
| Phosphotungstic acid | 500 po | 4/8 | 4/8 ^d | complexing agent |
| " | 1000 po | 8/8 | 4/8 ^d | |
| " | 1000 po | 8/8 | 1/8 ^d | |
| Phosphomolybdic acid | 500 po | 4/8 | 4/8 ^d | complexing agent |
| " | 1000 po | 6/8 | 4/8 ^d | |
| Potassium ferrocyanide | 100 ip | 6/8 | 7/8 ^c | complexing agent |

dose (mg/kg) of paraquat ; a) 100 b) 141 c) 200 d) 300

SUMMARY

C EFFECT OF VARIOUS COMPOUNDS AS A POSSIBLE ANTIDOTE ON PARAQUAT POISONING

Animals ; Male dd mice, 5-7 weeks old

Chemicals ; Paraquat (96 % purity)

Various compounds as possible antidote

Methods ; Mice were given 100-300 mg/kg amount of paraquat as aqueous solution, a single dose. After 1 hour, the antidote was administered orally or intraperitoneally to one group, and mice were observed for 7-14 days. The effectiveness of the antidote was assessed by comparing the group given the antidote with the one given paraquat only. The results are summarized in the following table.

| compounds | dose (mg/kg) | | survived animals | | pharmacological action to be expected |
|--------------------|-------------------|----|------------------|-------------------|--|
| | | | with antidote | paraquat only | |
| Cystein | 100 | ip | 0/8 | 1/8 ^c | radical scavenger antioxidant for lipid |
| " | 100 | ip | 2/8 | 5/8 ^a | |
| Methionine | 100 | ip | 4/9 | 6/9 ^b | improvement of lipid metabolism |
| Glutathione | 100 | ip | 5/8 | 5/8 ^a | radical scavenger antioxidant for lipid |
| " | 200 | ip | 0/10 | 0/10 ^c | |
| " | 20x5 | ip | 2/9 | 4/9 ^d | |
| Erithorbic acid | 200 | ip | 0/10 | 0/10 ^c | antioxidant for lipid |
| " + Hesperidin | 200+200 | ip | 0/8 | 1/8 ^c | capillary stabilizer |
| α-Tocopherol | 500 | po | 2/9 | 5/9 ^b | radical scavenger antioxidant for lipid |
| Ca-EDTA | 200 | ip | 0/8 | 1/8 ^c | antioxidant for lipid |

dose (mg/kg) of paraquat ; a) 100 b) 141 c) 200 d) 300

Emetic Submission
A. FDA

AC



Chevron Chemical Company
940 Hensley Street, Richmond, CA 94804

June 10, 1977

Subject: PP-796

Found in PQ
Emetic + steroids
Correspondence
Registry.

Tox data
Emetic
Submission to
FDA.

Mr. Rudolph Apodaca, Director
Division of Drug Labeling and Compliance HFD-310
Bureau of Drugs
5600 Fishers Lane
Rockville, Maryland 20857

Dear Mr. Apodaca:

The Pesticide Registration Division, Office of Pesticide Programs, advises us that we should seek FDA comments on the possible need to obtain a new drug clearance for 2-amino-4,5-dihydro-6-methyl-4-propyl-s-triazolo(1,5-d)-pyrimidin-5-one (also referred to as PP-796 and ICI 63,197). PP-796 is being proposed for use at not more than 0.1% in paraquat dichloride herbicide formulations as a pesticidally inert ingredient. The purpose is to induce vomiting in cases of oral ingestion. Because of the proposed use we and the Environmental Protection Agency are interested in obtaining your opinion as to whether or not PP-796 would, in this instance, qualify as a drug and require a new drug clearance.

Since paraquat dichloride formulations are registered as pesticides under the Federal Insecticide, Fungicide, Rodenticide Act, we submitted a petition to the Environmental Protection Agency on April 1 for an exemption of PP-796 under CFR 180.1001(d) as an inert ingredient for exclusive use in paraquat herbicide formulations. A copy of our April 1 letter and a summary of data submitted to support a clearance as an inert ingredient are attached in Appendix A. Pertinent information on the toxicology and medical treatment of paraquat are included in Appendix B. Human and experimental animal data indicate that the addition of PP-796 to paraquat herbicide formulations will reduce the oral toxicity of the new formulations and increase the likelihood of successful treatment of oral ingestion poisoning cases.

It is our opinion that the proposed use of PP-796 should not require a new drug clearance for the following reasons:

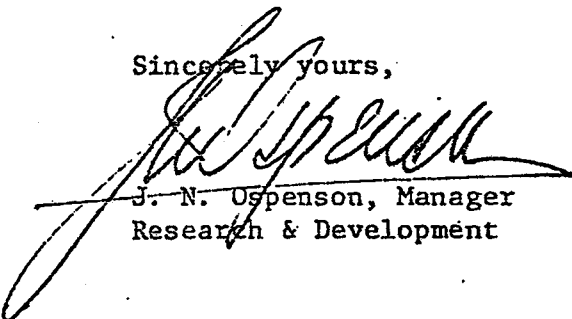
1. PP-796 will not intentionally be used as a drug.
2. Humans will only directly ingest pharmacologically active doses of PP-796 as a consequence of suicidal or accidental ingestion of a potentially fatal level of paraquat.
3. There is no reasonable expectation of pharmacologically significant residues of PP-796 in human foods.

June 10, 1977

4. Neither Chevron nor Imperial Chemical Industries have any intentions of marketing PP-796 as a drug.
5. We do not have any plans to incorporate PP-796 in other non-paraquat products as we feel this is a unique situation.
6. Our proposed wording for the regulation under CFR 40 180.1001 (d) will permit adequate control of the use of PP-796.

We look forward to your opinion as to whether or not a new drug clearance would be required for the proposed use of PP-796 in paraquat dichloride herbicide formulations.

Sincerely yours,



J. N. Ospenson, Manager
Research & Development

FXK:sag



Chevron Chemical Company
940 Hensley Street, Richmond, CA 94804

April 1, 1977

Environmental Protection Agency
Registration Division. HM-567
Room E-347
Washington, D.C. 20460

Gentlemen:

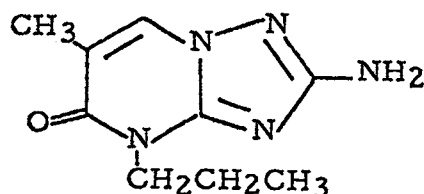
We are interested in obtaining clearance for listing 2-amino-4,5-dihydro-6-methyl-4-propyl-s-triazolo (1,5-a) pyrimidin-5-one (also referred to as PP-796 and ICI 63,197) under 40CFR180.1001(d) as an inert ingredient for exclusive use as an emetic at not more than 0.1% in paraquat dichloride herbicide formulations. As outlined by Pesticide Information Sheet 16 (February 21, 1974), the following information on 2-amino-4,5-dihydro-6-methyl-4-propyl-s-triazolo (1,5-a) pyrimidin-5-one is herewith included:

1. Chemical name (trade names are not listed) and any specifications needed to adequately identify the material.

Chemical Name: 2-amino-4,5-dihydro-6-methyl-4-propyl-s-triazolo (1,5-a) pyrimidin-5-one. This conforms to IUPAC nomenclature. Alternate chemical name is 2-amino-6-methyl-5-oxo-4-N-propyl-4,5-dihydro-s-triazolo (1,5-a) pyrimidine.

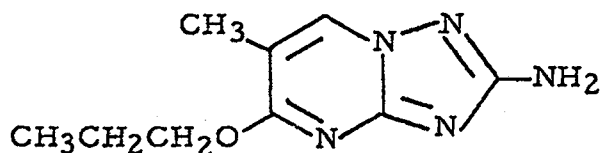
Formula: $C_9H_{13}N_5O$

Structural Formula:



Molecular Weight: 207.2

Purity: Technical PP-796 has a purity greater than 90%. The main impurity is the 5-oxypropyl derivative, coded ICI 69,631.



Physical State: A white to pale cream powder.

Melting Point: 163-165°C

Vapor Pressure: Negligible

Solubility: Soluble in 500 parts of water, in 12 parts of chloroform and 170 parts of 95% alcohol.

Odor: None

Stability: Stable at room temperature (27°C) for seven years.

DOT Label Required: Not determined. Not presently manufactured or available in the United States.

Compatibility: Compatible with and stable in aqueous solutions of paraquat herbicide formulations. Gramoxone (a paraquat formulation marketed by Imperial Chemical Industries Limited, Great Britain, which contains 200 g paraquat cation per liter - as the dichloride salt-equivalent to 2.0 lb. cation per gallon) containing PP 796 has been stored in representative sales containers (rigid PVC) for 3 months at 50°C and for 6 months at -5°, 0°, 25° and 37°C. There has been no evidence of physical damage or loss of chemical activity. This formulated product has a density of 1.095 ± 0.02 g/cc; it is non-volatile and non-flammable.

2. The paragraph or paragraphs (c, d or e) of 180.1001 in which listing is desired.

40CFR180.1001(d)

3. A description of the use of the material in pesticide formulations including the proportion (maximum) and any limitations.

For exclusive use as an emetic at not more than 0.1% in paraquat dichloride herbicide formulations.

INCLUDED WITH THIS REQUEST AND CONSTITUTING A PART OF THIS SUBMISSION ARE PERTINENT UNPUBLISHED RESEARCH REPORTS OF PP-796 WHICH PROVIDE INFORMATION ON: FORMULATION ANALYSIS; RESIDUE ANALYSIS; APPLICATION AND USE INFORMATION; RESIDUE DATA; TAINT TRIALS; PERSISTENCE DATA IN SOIL, PLANTS AND WATER; EXPERIMENTAL TOXICOLOGY DATA IN ANIMALS; HUMAN CLINICAL TRIALS; AND FIELD OBSERVATIONS OF SPRAY APPLICATORS.

4. Available residue data and/or information on volatility or other dissipation factors.

The stability of PP-796 has been evaluated after 3 months storage at 50°C and for 6 months at -5°, 0°, 25° and 37°C. There was no evidence of physical change or loss of chemical activity.

A method is available for determination of PP-796 in aqueous solutions. The determination of paraquat residues in crops is unaffected by PP-796. PP-796 residues can be determined quantitatively in ryegrass and potatoes by means of gas-liquid chromatography. The limit of detection of PP-796 by this residue method is 0.02 ppm.

PP-796 is not a pesticide and has been shown to be herbicidally inert and does not affect the weed killing properties of paraquat. PP-796 is extensively degraded by sunlight in aqueous solutions and is poorly degraded by hydrolysis in water. Persistence studies demonstrate that PP-796 is extensively degraded by plants and soil.

Taint trials indicate that PP-796 does not affect the flavor of fresh or cooked samples of paraquat/PP-796 in treated potatoes.

5. Available toxicity data.

Acute and subacute toxicity studies, teratogenic and oncogenic evaluations have been generated with PP-796 in experimental animals. Trials in pigs, dogs and monkeys demonstrate the emetic effectiveness. Human clinical trials, supported by data from experimental animals, demonstrate that the amount of PP-796 required to induce vomiting in the majority of humans ingesting it is 5 mg (0.08 mg/kg in a 60 kg man).

Observations on field applicators indicate no adverse effects were noted from spraying PP-796. It is estimated that the airborne concentrations of PP-796 in agricultural sprays would not reach levels to cause pharmacological effects in field applicators, even if used at concentrations of four times the recommended label rate.

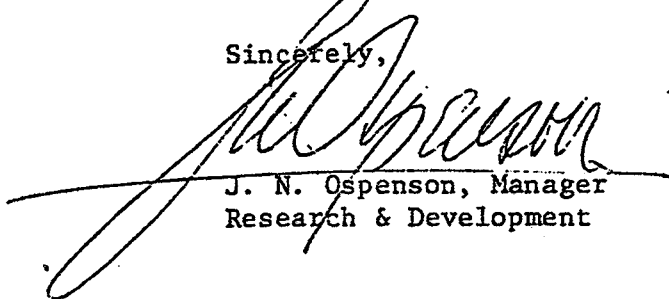
6. Prior approvals as food additives, drugs, cosmetics, etc., if any.

PP-796 has not been approved for use in the United States. However, in August 1976, The Ministry of Agriculture, Great Britain, granted a limited clearance to the Plant Protection Division of Imperial Chemical Industries, Limited, Great Britain, permitting the use of a formulation of Gramoxone (paraquat concentrate) containing 0.05% of PP-796 emetic in the United Kingdom. On December 1, 1976, Imperial Chemical Industries, Limited, petitioned the Ministry of Agriculture requesting commercial clearance of the Gramoxone + PP-796 emetic product. This petition was approved on February 25, 1977 by the Ministry of Agriculture and Imperial Chemical Industries was granted a Provisional Commercial Clearance for a three-year period. In addition, Imperial Chemical Industries, Limited,

plans to apply for clearance of PP-796 as an emetic in paraquat herbicide formulations throughout West European countries and, ultimately the world, as experience is gained and supplies become available.

Based on human and animal experimental data it is anticipated that the addition of PP-796 emetic to paraquat dichloride herbicide formulations will not only reduce the hazard of the new formulation but that it may represent a significant step in improving the chance of survival following paraquat ingestion. We look forward to obtaining a clearance for listing 2-amino-4,5-dihydro-6-methyl-4-propyl-s-triazolo (1,5-a) pyrimidin-5-one (PP-796) as an inert ingredient in paraquat dichloride herbicide formulations under 40CFR180.1001(d).

Sincerely,



J. N. Ospenson, Manager
Research & Development

FXK:sag

SUMMARY

OF

DATA TO SUPPORT CLEARANCE FROM THE EXEMPTION FROM THE REQUIREMENT OF A TOLERANCE FOR 2-AMINO-4,5-DIHYDRO-6-METHYL-4-PROPYL-5- TRIAZOLO (1,5-a) PYRIMIDIN-5-ONE (PP 796) FOR EXCLUSIVE USE AS AN EMETIC IN PARAQUAT HERBICIDE FORMULATIONS UNDER 40CFR180.1001(d)

A broad series of investigations have been conducted with PP 796 emetic. These investigations include stability studies, formulation analysis, residue analysis, taint trials, persistence studies, acute and subacute toxicity studies, mutagenic and teratogenic investigations, metabolism studies, pharmacological investigations, emesis trials in experimental animals, and human clinical trials.

The following is a summary of these investigations with PP 796.

NOTE: Reference is frequently made in this submission to Gramoxone, JF 6043, and JF 6044. Gramoxone is a product of Imperial Chemical Industries Limited, Great Britain, and contains 200 g paraquat cation per liter (as the dichloride salt -equivalent to 2.0 lbs cation per gallon) and 5% surfactant or wetting agent. JF 6043 is a formulation containing 200 g paraquat cation per liter, plus 1% pyridine base stench, 0.05% PP 796 and 10% surfactant or wetting agent. JF 6044 is similar to JF 6043, but contains only 5% surfactant or wetting agent. ORTHO Paraquat CL contains 239.8 g paraquat cation per liter (equivalent to 2.0 lb active per gallon) and 10% of a surfactant or wetting agent.

| <u>Method of Manufacture</u> | <u>Reference Numbers</u> | <u>Page Number</u> |
|---|------------------------------|------------------------|
| A four-step method of PP 796 manufacture is outlined. Evidence of molecular structure is also presented. | 1 | 5-9 |
| <u>Stability Studies With PP 796</u> | | |
| Storage of purified PP 796 in clear glass, foil-lined screw-capped containers in the light at 25°C (room temperature), in the dark at 4°C, 37°C, and 50°C, or to a relative humidity of 78% at room temperature and 37°C indicate that PP 796 is stable to light and is not hygroscopic after a 12 month storage period. The results obtained to date indicate that the drug will be stable for at least three years under normal storage conditions. | 1 | 16-20 |
| <u>Formulation Analysis of Paraquat and PP 796</u> | | |
| The current method for the determination of paraquat in aqueous solutions is unaffected by the addition of PP 796. PP 796 is determined by a flame ionization gas chromatographic method. | 2 | 39-42 |
| <u>Residue Analysis of Paraquat and PP 796</u> | | |
| The determination of paraquat residues in crops is unaffected by the addition of PP 796. | 3 | 43-82 |

PP 796 residues can be determined quantitatively in ryegrass and potatoes by means of gas liquid chromatography. Extracts are obtained from crop samples by maceration with cold methanol. The extracts are cleaned up by solvent partition and/or column chromatography using silica gel. Determination of PP 796 is by gas-liquid chromatography, using a nitrogen selective detector. The lower limit of detection of PP 796 by this method is 0.02 ppm.

Residue Data

Potatoes have been sprayed overall with 6 litres of a formulation of 'Gramoxone' containing 500 mg PP 796 per litre for weed control. The crop was 25-90% emerged at the time of spraying. Analysis of tubers harvested 6-14 weeks after spraying yielded no detectable residues of PP 796.

3

43-82

Ryegrass treated at 3.0 and 6.0 l/ha with a similar formulation of 'Gramoxone' plus PP 796 at 500 mg/litre contained PP 796 residues of 0.04-0.11 ppm and 0.09-0.26 ppm, respectively, on the day of treatment. These levels had subsided to 0.02-0.03 and 0.02-0.05 ppm 7-8 days after application. A further trial, in which 'Gramoxone' containing 2,000 mg PP 796 per litre was applied at 6.0 l/ha, yielded no detectable residues of PP 796 5-6 weeks after application. PP 796 levels, where detectable, are considered to be without toxicological significance.

Taint Trails

The taint potential of 'Gramoxone' formulations containing stench and stench plus PP 796 have been compared in a trial at the Campden Food Preservation Research Association. Potatoes, variety Maris, Peer, were sprayed on 14th May, at emergence, with 11.2 liters of one or other of the two formulations per hectare. Tubers were lifted on 21st July and subjected to the Association's standard taint tests. Neither fresh cooked nor canned samples showed any statistically significant difference in taste.

4

83

Soil Persistence

Radio labelled ¹⁴C-PP 796 has been applied to soils under both aerobic and anaerobic conditions and in the presence and absence of 'Gramoxone' (containing 1% pyridine base). Less than 2.5% of applied radioactivity was evolved as volatile ¹⁴C-labelled products irrespective of soil type and the presence of 'Gramoxone'. Amounts of radioactivity extracted decreased with time, indicating a degree of binding.

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84-106

Persistence in Plants

^{14}C -PP 796 applied at approximately 75 ppm to cotton leaves in the greenhouse degraded slowly so that after 28 days only 25-30% of the applied radioactivity (40% of the radioactivity recovered) was present as PP 796.

6

107-126

Up to 35% of the applied radioactivity was lost from the leaves. Of the remainder, 15-20% could not be extracted and approximately 20% was present as polar products.

Water Persistence and Stability

The stability of ^{14}C -labelled PP 796 in water has been assessed using concentrations of 5 ppm with and without 'Gramoxone'. Unlabelled PP 796 was tested at 500 ppm in a 4% acetone/water solution. These aqueous solutions were rapidly degraded in bright sunlight, with a half-life of approximately 4 days. The rate was unchanged by the use of different sensitizers (i.e. 'Gramoxone', acetone) although the pattern of degradation products changed. One or two major and numerous minor products of photodegradation resulted.

7

127-165

PP 796 has been applied at 5 and 50 ppm, both with and without stetched 'Gramoxone' to river waters high in microbial content. Population changes within the limits of natural fluctuation occurred during incubation, but PP 796 had no effect on total microbial levels.

The hydrolysis of ^{14}C -PP 796 in sterile, deionized glass-distilled water at pH levels of 5, 7 and 9 kept in the dark at 25°C has been investigated. Concentrations of 5 and 50 ppm showed no significant degradation after 26 days, when approximately 90% of the applied radioactivity was recovered, approximately 95% of which was as PP 796.

These results show that PP 796 is extensively degraded by sunlight in aqueous solutions and is poorly degraded by hydrolysis in water within pH limits normally encountered naturally, in soil and on plant surfaces. PP 796 had no effect on microbial populations in two representative river waters.

Acute Toxicity to Vertebrates

(a) Oral and Intravenous Toxicity

The following acute LD₅₀ values have been established.

8A

2-9

| <u>Species</u> | <u>Route</u> | <u>LD50 (mg/kg)</u> |
|----------------|--------------|---------------------|
| Rat | Oral | 150-155 |
| Mouse | Oral | 300-310 |
| Rat (female) | Intravenous | 50-60 |
| Rat (male) | Intravenous | 60-75 |
| Mouse | Intravenous | >150 |

The acute oral LD₅₀ of JF 6043 to both male and female dogs was estimated to be 0.5-1 ml/kg, equivalent to 100-200 mg paraquat cation/kg.

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330-332

The LD₅₀ of paraquat to monkeys has been shown to be approximately 60-70 mg/kg body weight. The presence of an emetic dose of PP 796 raises this value to 250-500 mg/kg body weight.

10

333-345

(b) Skin Absorption Properties of JF 6043

Studies with JF 6043 have shown the acute dermal LD₅₀ to female rats to be 0.373 ml. formulation per kg (equivalent to 75 mg paraquat ion/kg).

9

330-332

(c) Skin Irritation and Sensitization Potential

PP 796 0.3% cream and PP 796 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. Mild erythema was observed in guinea pigs after 12 applications of PP 796 0.3% cream and PP 796 3.0% ointment.

11

372-389

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 sensitization in the rabbits.

| | Reference Numbers | Page Numbers |
|---|----------------------|--------------------|
| Three consecutive daily applications of a 1:40 aqueous dilution of JF 6043 to female rats under an occlusive dressing for 24 hours caused moderate erythema and slight desquamation followed by some scabbing. Irritation was still present ten days after the third application. The diluted formulation is described as a moderate irritant to rat skin. | 9 | 330-332 |
| (d) <u>Eye Irritation Properties of JF 6043</u> | | |
| Instillation of 0.1 ml of the undiluted formulation into the left eyes of a group of six female albino rabbits produced corneal opacity, iritis and pannus which persisted at 7 days. | 9 | 330-332 |
| <u>Subacute Effects to Vertebrates</u> | | |
| (a) <u>18-Day Oral Administration - Rats</u> | | |
| Two groups of rats were given PP 796 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. | 8A | 180 |
| (b) <u>39-Day Oral Administration - Dogs</u> | | |
| Two dogs were given daily increasing oral doses of PP 796 from 0.1 mg/kg to 1.5 mg/kg over 36 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. | 8A | 181 |
| (c) <u>90-Day Feeding - Rats</u> | | |
| Three groups of rats were fed 0.25, 1.25 and 5 mg PP 796/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. | 8A, 8B | 182-186 259-326 |
| 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.

8A, 8B

There were no histological changes attributable to PP 796 in the rats left for twelve weeks.

(d) 90-Day Feeding - Dogs

Three groups of dogs were fed 0.15; 0.5 and 1.5 mg PP 796/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.

8A, 8B

187-192

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 PP 796 were found in the dogs.

Teratogenic Investigations in Rabbits and Rats

Female proven rabbits were dosed orally with 0.25, 0.75 and 1.25 mg PP 796/kg on days 6-18 of pregnancy, and female rats were fed 0.25 and 1.25 mg PP 796/kg on days 6-15 of pregnancy inclusive.

8A, 8B

194-201,
326-329

Both rats and rabbits dosed at 1.25 mg/kg showed signs of maternal toxicity, i.e. 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 PP 796 has no teratogenic effects at doses used and has little significant effect on pregnancy, littering or weaning.

Mutagenic Evaluation (Ames Salmonella Assay)

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|---|----|---------|
| PP 796 was not mutagenic to four tester strains of <u>Salmonella typhimurium</u> in the Ames reverse mutation test. | 12 | 419-427 |
|---|----|---------|

Oncogenic Evaluation in Mice

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|---|----|---------|
| Mice were fed dietary levels of 5 ppm or 20 ppm ICI 63,197 (corresponding to 1.25 and 5 mg/kg/day, respectively) for seventy eight weeks. Survival was comparable to untreated controls. A dose related reduction of body weight occurred which assumed statistical significance at the highest dose level. | 13 | 428-610 |
|---|----|---------|

The total incidence of tumors in each group and the incidence in particular organ systems showed no biologically significant difference between the control and treated mice. It is concluded that ICI 63,197 has no tumorigenic potential in this strain of mice.

Metabolism Studies in Vertebrates

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| ¹⁴ C-labelled PP 796 has been dosed orally to rat, mouse, guinea pig, beagle and rhesus monkey. The greater part of the radio-activity 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 PP 796. 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 PP 796. It constituted 33-38% of the total ¹⁴ C administered to the rhesus monkey, guinea pig and dog, and 15% in the rat. | 14 | 684-700 |
|--|----|---------|

Pharmacology of PP 796

| | | |
|--|----|---------------------|
| The effects of PP 796 on the central nervous system, anti-bronchoconstrictor activity, anaphylactic shock potential in guinea pigs and mice, cyclic 3',5'-AMP phosphodiesterase activity, general pharmacological reactions, and serum concentrations in dogs and rats after oral administration have been investigated. | 14 | 612-641, 663-700 |
|--|----|---------------------|

| | | |
|---|----|---------|
| Pharmacologically PP 796 is a phosphodiesterase inhibitor. It increases the resting levels of cyclic AMP in the guinea pig lung and kidney. | 14 | 660-662 |
|---|----|---------|

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|--|----|---------|
| In tests with perfused isolated guinea pig lung, PP 796 at a concentration of 5 ug/ml inhibited almost completely the histamine released following injection of antigen. At lower doses the effect was extremely variable. PP 796 is active against bronchospasm induced by a large dose of histamine. | 14 | 642-659 |
|--|----|---------|

On this pharmacological basis the compound was investigated (as ICI 63,197) for the control of asthma in man. The human emetic response prevented further therapeutic development. The maximum tolerated non-emetic dose of PP 796 in monkeys and marmosets appears to be in the range of 0.1 to 0.5 mg/kg.

Acute oral studies in the vomiting species dog and monkey have demonstrated that PP 796 added to paraquat concentrations several times in excess of the LD₅₀ to these species induced vomiting. This resulted in survival provided that it occurred within an hour of dosing. The concentration of paraquat in the plasma of animals given paraquat plus PP 796 was markedly lower than that of animals given paraquat alone. The toxicity to monkeys of paraquat formulated in the presence of an emetic dose of PP 796 was estimated to be lowered by a factor of approximately five.

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| 10 | 333-345 |
|----|---------|

Effects on Man - Human Clinical Trials

PP 796, as ICI 63,197, was granted a Clinical Trials Certificate (No. CDS/29/77) to Imperial Chemical Industries, Limited on 23 October 1970. This was converted to Clinical Trials Certificate of Right (No. 0029/0077) on 5 August 1974.

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| 11, 15 | 346-359, 701-752 |
|--------|---------------------|

In clinical trials PP 796 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 PP 796 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 PP 796 in man was between 1½ and 3½ hours.

Biological Availability

(a) Serum Levels in Dogs After Topical Application

PP 796 0.3% cream and 3.0% ointment were applied to the intact and abraded skin of beagle dogs. The dosage levels applied were as follows: 0.3% cream - 2.3 to 2.8 mg/kg to intact skin and 2.7 to 3.3 mg/kg to abraded skin; 3.0% ointment - 6.9 to 11.1 mg/kg to intact skin and 6.9 to 10.4 mg/kg to abraded skin. These studies demonstrated that PP 796 can penetrate intact dog skin and that a greater degree of absorption is obtained when the stratum corneum is damaged. No adverse reaction was seen in any of the animals.

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|----|---------|
| 11 | 372-379 |
|----|---------|

(b) Serum Levels in Humans After Topical Application

PP 796 0.3% cream and 3.0% ointment were rubbed into the volar surface of the forearm. One group of four volunteers were initially treated with 0.5 g of 0.3% cream and two days later were treated with 1 g of 0.3% cream. Another group was similarly treated with the 3.0% ointment using the same dosage schedule. No PP 796 was detected in the blood of the eight subjects.

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379-380

Two subjects noted a minor tingling sensation at the site of application following application of 1 g of the ointment. One subject noted a vague metallic taste following application of 0.5 and 1 g of the ointment. No signs of local irritancy were observed.

Estimated Effective Emetic Dose in Man

It has been demonstrated in man, supported by data from experimental animals, that the amount of PP 796 required to induce vomiting in the majority of humans ingesting it is 5 mg (0.08 mg/kg in a 60 kg man). The minimum dose of 'Gramoxone' known to cause death is 10 ml. JF 6044 has thus been formulated to contain 5 mg PP 796 in 10 ml product.

16

753-760

Emetic Trials in Pigs, Monkeys and Marmosets

The minimum effective emetic dose of PP 796 is 0.5 to 1.0 mg/kg in pigs and approximately 0.6 mg/kg in monkeys and marmosets.

17

761-771

Occupational Observations in Field Applicators

During large scale field trials in stubble, observations were made on the men engaged in spraying. No adverse effects were noted resulting from use of PP 796.

18

772-777

As 'Gramoxone' is used widely through knapsack sprayers, the chance that PP 796 may produce adverse side effects, such as nausea and vomiting, under normal working conditions has also been examined. It was concluded that the level of PP 796 in the atmosphere around an operator's face would never reach a significant level, even if used at a concentration of 2% (four times the normal rate).

Medical Data

Apart from the induction of vomiting, the symptoms and treatment of cases of oral ingestion of 'Gramoxone' with PP 796 will be as for paraquat itself and are well documented. Based on human and experimental animal data it is optimistically predicted that the addition of PP 796 to 'Gramoxone' will not only reduce the toxicity of the new formulation but that it will increase the likelihood of successful treatment of cases of oral ingestion.

Field Observations (Wildlife)

No cases of harm to animals or wildlife have been reported following the spraying of some 1,000 hectares during evaluation trials in the United Kingdom. The 96-hour LC₅₀ of PP 796 to rainbow trout is 40 ppm.

19

778-

1. SPECIFICATIONS

1.1 SYSTEMATIC NAME : 2-amino-4,5-dihydro-6-methyl-4-propyl-S-triazolo (1,5-a) pyrimidin-5-one.

1.2 FORMULA

1.2.1 Empirical : $C_9H_{13}N_5O$

1.2.2 Structural :

STRUCTURE'S
STILL TO GO
IN.

+ here

1.3 MOLECULAR WEIGHT : 207.2

1.4 MANUFACTURERS CODE NO : ICI 63,197
PP 796

1.5 PURITY : Technical grade PP796 is greater than 90% pure.
The main impurity is the 5-oxypropyl derivate:

ⓧ

- 1.6 APPEARANCE : White/Cream crystalline powder
- 1.7 ODOUR : No odour
- 1.8 MELTING POINT : 163-165°C
- 1.9 COMPATIBILITY : PP796 is compatible with and stable in aqueous solutions of paraquat.

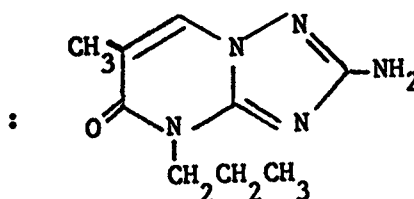
NAMES

- (i) Approved Name : Not yet selected
- (ii) Laboratory Code Number : I.C.I. 63,197
- (iii) Chemical Name : 2-Amino-6-methyl-5-oxo-4-n-propyl-4,5-dihydro-s-triazolo (1,5-a) pyrimidine

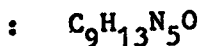
DESCRIPTION

- (i) Physical form : A white to pale cream powder
- (ii) Solubility : Soluble in 500 parts of water, in 12 parts of chloroform and in 170 parts of alcohol (95%).

(iii) Structural formula



(iv) Molecular formula



(v) Molecular weight

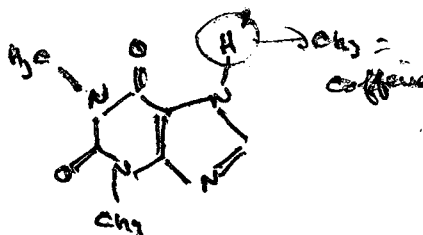
: 207.2

5. INTENDED USE

Evaluation of efficacy in the disease.

Theophylline
 $C_7H_8N_4O_2 \cdot H_2O$
198.2
 H_2O sol. 8 mg ml⁻¹

piratory



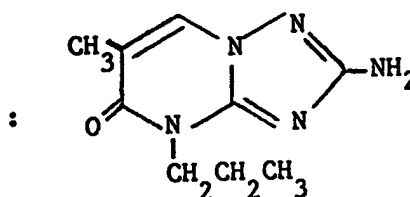
NAMES

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DESCRIPTION

- (i) Physical form : A white to pale cream powder
- (ii) Solubility : Soluble in 500 parts of water, in 12 parts of chloroform and in 170 parts of alcohol (95%).

(iii) Structural formula



(iv) Molecular formula

: C₉H₁₃N₅O

(v) Molecular weight

: 207.2

5. INTENDED USE

Evaluation of efficacy in the treatment of mental disease and respiratory disease.

2. TOXICITY

2.1 ACUTE TOXICITY

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.

2.2 SUBCHRONIC TOXICITY

2.2.1 Sighting Tests (Rat and Dog)

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.

2.2.2. Three Month Feeding Study (Rat)

Ninety Alderly Park Strain 1 rats were maintained throughout the test on the usual stock diet; they were divided into four groups. Group 1 consisted of ten male and ten female rats each dosed orally with vehicle only daily for three months. Group 2 consisted of fifteen male and fifteen female rats each dosed orally with 5mg PP796/kg daily for three months. Group 3 consisted of ten male and ten female rats each dosed orally with 1.25mg PP796/kg daily for three months. Group 4 consisted of ten male and ten female rats each dosed orally with 0.25mg PP796/kg daily for three months.

2.2.3 Three Month Feeding Study (Dog)

Thirty-two beagles were randomly divided into groups of four males and four females and maintained throughout the test on the usual stock diet. Group 1 were controls dosed orally with placebo daily for three months. Group 2 were dosed orally with 0.15mg PP796/kg daily for three months. Group 3 were dosed orally with 0.5mg PP796/kg daily for three months. Group 4 were dosed orally with 1.5mg PP796/kg daily for three months.

These paragraphs will be used directly below
the relevant headings

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 2 1/2 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.

2.2.2 Three Month Feeding Study (Rat)

dosed orally with
~~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.

blood samples taken from
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.

2.2.3 Three Month Feeding Study (Dog)

dosed orally with
~~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.

and Rat

X 2.2.4 Teratogenicity (Rabbit)

X
Deviation study? → 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. ~~only treated with~~

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.

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

Forty-eight female proven rabbits were divided into four groups of twelve. Group 1 (control) were dosed orally with "Dispersol" on days 6-18 of pregnancy inclusive. Group 2 were dosed orally with 0.25mg PP796/kg on days 6-18 of pregnancy inclusive. Group 3 were dosed orally with 0.75mg PP796/kg on days 6-18 of pregnancy inclusive. Group 4 were dosed orally with 1.25mg PP796/kg on days 6-18 of pregnancy inclusive.

Sixty pregnant rats were divided into three groups of twenty. Group 1 (control) were dosed orally with "Dispersol" on days 6-15 of pregnancy inclusive. Group 2 were dosed orally with 0.25mg PP796/kg on days 6-15 of pregnancy inclusive. Group 3 were dosed orally with 1.25mg PP796/kg on days 6-15 of pregnancy inclusive.

Half the animals (both rat and rabbit) in each group were killed before parturition (rats at 20 days and rabbits at 28 days) and the fetuses dissected for soft tissue change and then submitted for alizarin examination. The remaining animals in each group were allowed to litter and rear their young for three (rats) or four (rabbits) weeks. Any of the off-spring that died during this period were autopsied and fixed for alizarin examination those young that survived were killed and autopsied. 1

EXPERIMENTAL ANIMALS

MICE

The mice used in toxicity studies were from the Alderley Park Strain I, S.P.F. albino colony which has been bred at Alderley Park, Cheshire for ten years. They were housed ten to a cage and fed a standard pelleted diet made to our own specifications and water from an automatic drinking bottle. Diet and water were available ad libitum.

RATS

The rats used in toxicity studies were from the Alderley Park Strain I, S.P.F. albino colony which has been bred at Alderley Park, Cheshire for ten years. They were housed five to a cage and fed a standard pelleted diet made to our own specification and water from an automatic drinking bottle. Diet and water were available ad libitum.

RABBITS

The rabbits used in the toxicity studies were either Dutch cross or New Zealand White rabbits obtained from a local dealer. They were housed in individual cages and fed a pelleted diet made to our own specifications and water from an automatic drinking bottle. Diet and water were available ad libitum.

DOGS

The dogs used in the toxicity studies were beagles from a strain maintained at Alderley Park, Cheshire. They were housed in individual pens but dogs of the same sex were exercised together daily. They were fed twelve ounces of 'Dogstar' diet daily and water from an individual automatic drinking fountain was available ad libitum.

DOSAGE FORMS

I.C.I. 63,197 was administered to the laboratory animals as a ball milled dispersion in a non-toxic wetting agent in all cases except dogs which received tablets placed in hard gelatin capsules.

Toxicity in small animals

Suspensions of 0.1% w/v, 0.025% w/v and 0.005% w/v of I.C.I. 63,197 were prepared by ball milling the drug into the following solution :-

| | | |
|-----------------|--|--------|
| 'Lissapol' NX* | (Nonylphenoethyleneoxide condensate) | 0.1% |
| 'Lissapol' C* | (Sodium salt of sulphated cetyl/oleyl alcohol mixture) | 0.1% |
| 'Dispersol' OG* | (Polyglyceryl ricinoleate) | 0.1% |
| Water | to | 100.0% |

* Ex I.C.I. Dyestuffs Division

Toxicity in Dogs

Tablets containing 0.6, 5 and 6 mg. of active constituent.

| | <u>mg. per tablet</u> | | |
|--------------------|-----------------------|----------|----------|
| I.C.I. 63,197 | 0.6 | 5 | 6 |
| Lactose | 91 | 180 | 180 |
| Maize Starch | 7.4 | 13 | 12 |
| Magnesium stearate | <u>1.0</u> | <u>2</u> | <u>2</u> |
| Tablet weight | 100 mg. | 200 mg. | 200 mg. |

ACUTE TOXICITY

MICE

The compound was administered as a single dose by oral and intravenous routes to groups of ten male and ten female mice weighing between eighteen and twenty-two grammes. The animals were observed for fourteen days.

Oral administration

The drug was given by catheter as a suspension in a volume of 0.2 ml. Results are given in the table below:-

| Dose | Number dead/Total number | |
|-----------|--------------------------|---------|
| | Males | Females |
| 300 mg/kg | 4/10 | 4/10 |
| 310 mg/kg | 9/10 | 8/10 |
| 350 mg/kg | 10/10 | 9/10 |

The LD₅₀ is between 300 and 310 mg/kg.

Intravenous Administration

The drug was administered as a solution in a volume of 0.2 ml. Results are given in the table below:-

| Dose | Number dead/Total number | |
|-----------|--------------------------|---------|
| | Males | Females |
| 75 mg/kg | 0/10 | 0/10 |
| 100 mg/kg | 0/10 | 0/10 |
| 150 mg/kg | 5/10 | 3/10 |

Acute toxicity: mice

It was impossible to administer a larger dose than 150 mg/kg due to the insolubility of the compound. The LD₅₀ is greater than 150 mg/kg.

Toxic Signs

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

Many of the mice receiving the compound by intravenous administration developed a rapid rate of respiration immediately. The majority of the mice receiving 100 mg/kg and 150 mg/kg had convulsions within an hour after dosing, but many recovered. The mice which died did so within fifteen minutes of dosing.

No gross abnormalities were observed at autopsy.

RATS

The compound was administered as a single dose by intravenous and oral routes to groups of five male and five female rats weighing between one hundred and one hundred and forty-four grammes. The animals were observed for fourteen days.

Oral administration

The compound was given by catheter as a suspension in a volume of 0.5 ml. Results are given in the table below:-

| Dose | Number dead/Total number | |
|-----------|--------------------------|---------|
| | Males | Females |
| 100 mg/kg | 0/5 | 0/5 |
| 150 mg/kg | 0/5 | 1/5 |
| 155 mg/kg | 3/5 | 5/5 |
| 160 mg/kg | 5/5 | 5/5 |
| 175 mg/kg | 5/5 | 5/5 |
| 200 mg/kg | 4/5 | 4/5 |

The LD₅₀ is between 150 and 155 mg/kg both in males and females.

Intravenous administration

The compound was administered as a solution in a volume of 1 ml. Results are given in the table below:-

| | Number dead/Total number | |
|----------|--------------------------|---------|
| | Males | Females |
| 50 mg/kg | 2/5 | 2/5 |
| 60 mg/kg | 2/5 | 5/5 |
| 75 mg/kg | 4/5 | 5/5 |

The LD₅₀ in males is between 60 and 75 mg/kg and in females between 50 and 60 mg/kg.

Toxic Signs

Rapid respiration was seen immediately after dosing in the rats receiving the compound by oral administration. All of the animals which died did so from general inanition within forty-eight hours of dosing except for one animal which died after three days.

The rats receiving intravenous doses also developed a rapid respiration and salivated profusely within a few minutes of dosing. All the animals which died did so within the first twenty-four hours except for one animal which died after three days from general inanition.

No gross abnormalities were observed at autopsy.

RABBITSIntravenous administration

The compound was administered by intravenous injection to pairs of adult rabbits weighing between two and four kilogrammes. The compound was injected in the form of a solution (3ml/kg of body weight). The animals were then observed for fourteen days. Results are shown in the table below:-

| Dose | Number dead/Total number |
|----------|--------------------------|
| 5 mg/kg | 1/2 |
| 10 mg/kg | 1/2 |
| 20 mg/kg | 2/2 |
| 40 mg/kg | 2/2 |
| 60 mg/kg | 2/2 |

Toxic signs

The animals which died had convulsions and died within a few minutes of dosing. No abnormalities were seen in the rabbits surviving for the fourteen days.

3.

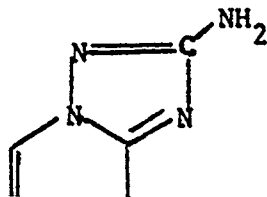
C¹⁴-labelled PP796 ~~has been~~ dosed orally to rat, mouse, guinea pig, beagle and rhesus monkey. The greater part of the radioactivity is excreted rapidly in the urine. A rhesus monkey vomited within 3 hours of receiving 0.08 mg/kg; the vomit contained 42% of the dose, of which at least 93% appeared to be unchanged PP796. ~~The~~ Monkey, rat, and guinea mouse 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 ¹⁴C ~~administered to~~ the rhesus monkey, guinea pig and dog, and 15% in the rat.

mouse, of that urine present in the urine of

DIVIDER

Introduction

I.C.I. 63,197 has been prepared in a labelled form with ^{14}C as shown below :



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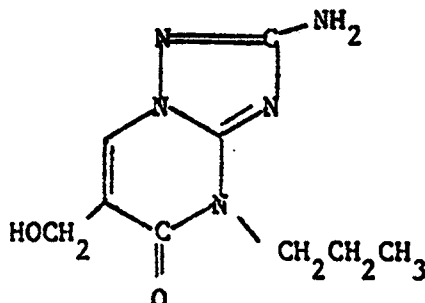
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in all species except rats, at least 70% of the dosed radioactivity is passed in urine within 48 hours. Rat differs from the other species in passing a large proportion (43%) of an oral dose in faeces; it has been shown that biliary excretion is of major importance in this species.

I.C.I. 63,197 is extensively metabolised in all species studied; one single non-conjugated major metabolite, I.C.I. 68,916, occurs in the urine of all the species, and has been identified and isolated in sufficient quantity for some of its properties to be evaluated.

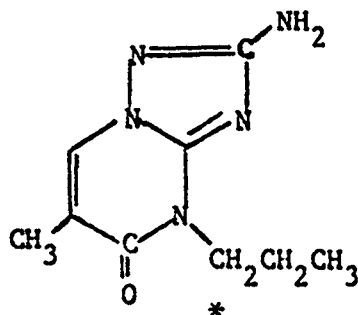


I.C.I. 68,916

The sera from rat, guinea-pig, and mouse contain only small amounts (4 - 7% of the total radioactivity in serum) of this metabolite;

Introduction

I.C.I. 63,197 has been prepared in a labelled form with ^{14}C as shown below :

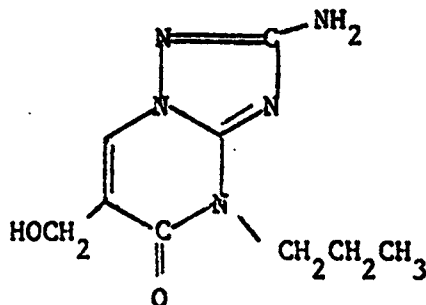


^{14}C I.C.I. 63,197

The labelled compound used in the experiments described below was shown to contain 98.2 - 98.8% I.C.I. 63,197, specific activity : 6.79 $\mu\text{Ci/mg}$.

^{14}C I.C.I. 63,197 was dosed orally to mice, rats, guinea-pigs, dogs, and rhesus monkeys. The excretion and distribution of labelled material have been studied. I.C.I. 63,197 is well absorbed after oral administration and in all species except rats, at least 70% of the dosed radioactivity is passed in urine within 48 hours. Rat differs from the other species in passing a large proportion (43%) of an oral dose in faeces; it has been shown that biliary excretion is of major importance in this species.

I.C.I. 63,197 is extensively metabolised in all species studied; one single non-conjugated major metabolite, I.C.I. 68,916, occurs in the urine of all the species, and has been identified and isolated in sufficient quantity for some of its properties to be evaluated.



I.C.I. 68,916

The sera from rat, guinea-pig, and mouse contain only small amounts (4 - 7% of the total radioactivity in serum) of this metabolite;

The tissue distribution curves in guinea-pigs show that maximum levels of radioactivity in serum and brain occur at about 1 hour after oral administration. The serum and tissue levels were found to be steady over the period $\frac{1}{4}$ to 4 hours after dosing.

48 hours after oral administration of ^{14}C I.C.I. 63,197 to a guinea-pig, the serum level was found to be 1% of the maximum level at 1 hour and only very low levels of radioactivity were detected in liver, kidney, bile, lung and heart.

Excretion

^{14}C I.C.I. 63,197 was dosed orally to small animals by catheter as an aqueous solution and to dogs and monkeys in capsules. Urine and faeces were collected separately and assayed for radioactivity. In Table 27, the total radioactivity found in urine and faeces is represented as a cumulative percentage of the dose.

Table 27. Excretion of radioactivity following oral administration I.C.I. 63,197

| Species : | Rat ♂ ^a | | Guinea-Pig ♂ ^b | | Mouse ♂ ^c | | Mouse ♂ ^d | | Dog ♂ | Rhesus Monkey ♀ |
|----------------------------|--------------------|------|---------------------------|------|----------------------|------|----------------------|-----|----------|-----------------|
| Dose mg/kg. | 2.1 | | 1.7 | | 12.9 | | 8.4 | | 0.25 | 0.04 |
| Time (hr.) | U | F | U | F | U | F | U | F | U (only) | U (only) |
| 4 | | | | | | | | | | 37.7 |
| 5 | | | | | | | | | | 51.3 |
| 6 | | | | | | | | | | 58.5 |
| 7 | 23.3 | 2.6 | 11.8 | 0.6 | 15.3 | | 21.8 | | | 65.7 |
| 24 | 55.0 | 21.5 | 63.5 | 1.8 | 66.3 | 9.1 | 67.7 | | 100.6 | |
| 31 | 57.3 | | 69.0 | | | | 70.6 | | | 98.6 |
| 48 | 59.4 | 41.6 | 73.6 | 11.8 | 69.6 | 10.6 | 74.4 | | 103.9 | 100.4 |
| 55 | | | 74.1 | | | | 75.0 | | 104.0 | 100.6 |
| 72 | 59.7 | 42.9 | 74.8 | 14.3 | 70.0 | 11.0 | 76.9 | 5.6 | 104.0 | |
| 96 | 59.8 | 43.2 | 75.0 | 15.0 | | | | | | |
| Total (U + F) ^e | 104.6 | | 90.0 | | 90.2 | | 90.9 | | 104.0 | 100.6 |

a : 1.6% dose in exhaled air in first 24hr.

b : no radioactivity detected in exhaled air

c : 9.2% dose in exhaled air in first 24hr.

d : 8.4% dose in exhaled air in first 24hr.

e : includes % dose in exhaled air where appropriate

U = Urine

F = Faeces

8.3 Urinary Metabolites

Urine samples from animals dosed orally with ^{14}C I.C.I. 63,197 were examined by thin-layer chromatography (T.L.C.) in chloroform/methanol (9 : 1) on Merck Silica GF plates. Urine samples from different species were found to contain the amounts of unchanged I.C.I. 63,197 and its metabolite, I.C.I. 68,916, indicated in Table 28.

Table 28. Proportions of I.C.I. 63,197 and its metabolite I.C.I. 68,916 in urine

| Species | Dose mg/Kg | Sample (hr) | % Dose in sample | % ICI 63,197 ^a | % ICI 68,916 ^a |
|-----------------|------------|-------------|------------------|---------------------------|---------------------------|
| Rat ♂ | 2.1 | 7-24 | 32 | 9.6 | 14.8 |
| Guinea-Pig ♂ | 1.7 | 7-24 | 52 | 2.9 | 36.8 |
| Dog ♂ | 0.25 | 0-24 | 100 | 1.0 | 33.0 |
| Rhesus Monkey ♀ | 0.04 | 0-4 | 38 | 3.0 | 38.1 |
| Mouse ♂ | 13.5 | 0-7 | 44 | 2.3 | 35.2 |

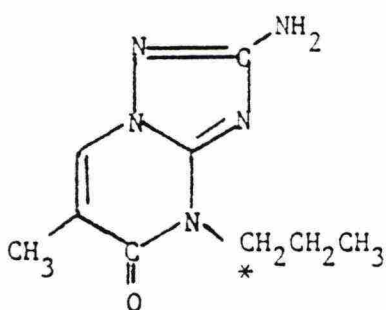
a : of the total radioactivity in the urine sample indicated.

Species differences

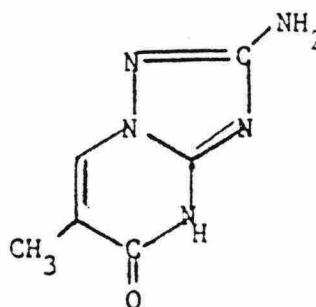
Urine samples from all species showed only two major fractions when examined by T.L.C.: I.C.I. 68,916 and polar (origin spot) material. The latter probably contains conjugates, but these have not yet been identified.

The rat produces a minor urinary metabolite (5% of the material in urine) whose molecular weight corresponds to that of I.C.I. 63,197 with an additional oxygen atom and an additional acetyl group. Its fluorescence spectrum ($\text{Ex}^{\text{n}}\lambda_{\text{max}}$ 285 nm; $\text{Em}^{\text{n}}\lambda_{\text{max}}$ 389 nm) is identical with that of N-acetyl I.C.I. 63,197 (I.C.I. 63,342). This minor metabolite has not been observed in urine from other species. But trace amounts of a labelled compound having the same T.L.C. properties have been found in chloroform extracts of mouse and guinea-pig serum.

The mouse excretes a significant proportion (9.2, 8.4 and 4.7% in 3 experiments) of an oral dose (8 - 14 mg./kg.) in exhaled air and in this respect differs from rat (1.6%) and guinea-pig (none detected). This could indicate dealkylation, but the dealkylated compound I.C.I. 65,329 has not been detected in urine from animals dosed orally with I.C.I. 63,197.



¹⁴C I.C.I. 63,197



I.C.I. 65,329

As rat, mouse, guinea-pig, dog and rhesus monkey all produce I.C.I. 68,916 as the single major non-conjugated urinary metabolite, these species have at least one major metabolic pathway in common. However, lack of information concerning the polar metabolites precludes further comparison at the present time.

4. EMETIC EFFECT

4.1 MODE OF ACTION

The following experimentally observed facts suggest a mode of action for PP796 as an emetic:

- (a) Emesis follows administration by any route.
- (b) Emesis is prompt and may even occur when blood levels following oral administration have not reached their peak.

(c) increase

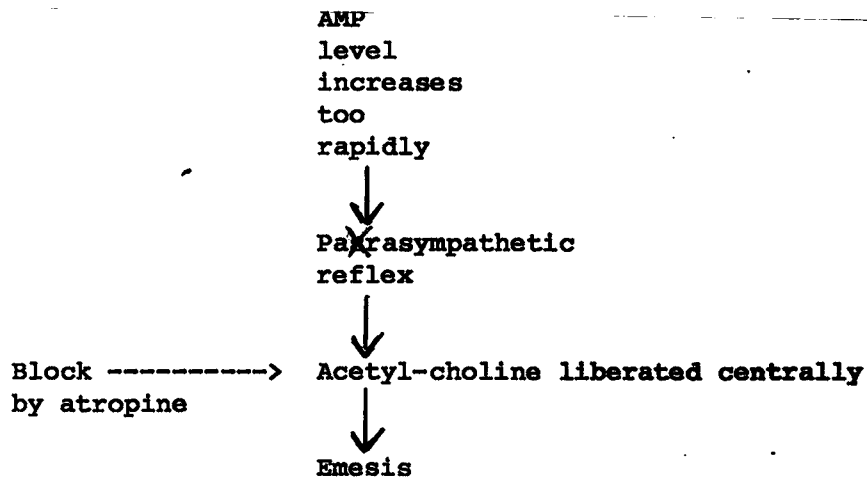
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4.2 EMETIC DOSE RESPONSE (DOG)

See report CTL/T/2459

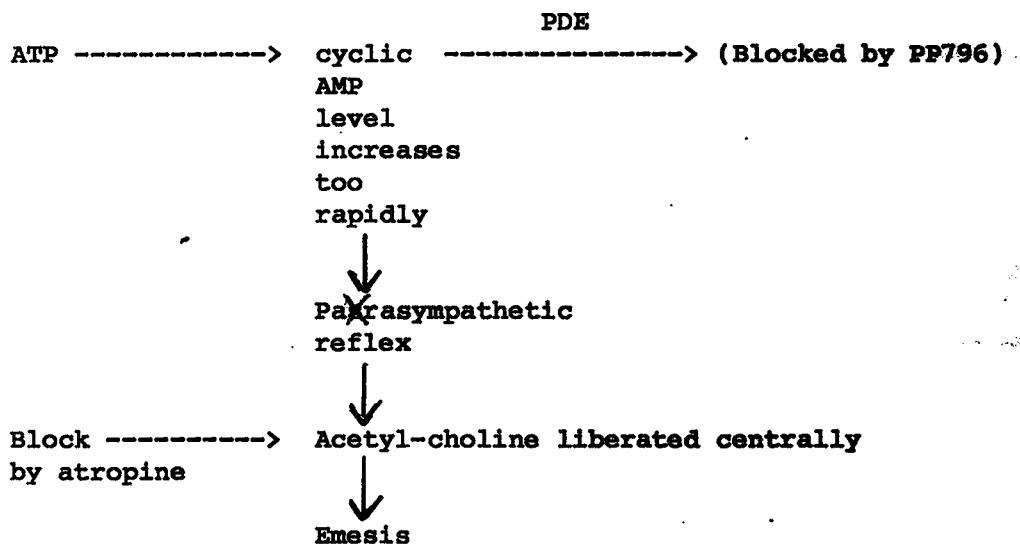
4. EMETIC EFFECT

4.1 MODE OF ACTION

The following experimentally observed facts suggest a mode of action for PP796 as an emetic:

- (a) Emesis follows administration by any route.
- (b) Emesis is prompt and may even occur when blood levels following oral administration have not reached their peak.
- (c) Emesis does not occur if the blood level is allowed to increase very slowly.
- (d) Emesis is inhibited by atropine, but not by more conventional anti-emetics such as anti-histamines.
- (e) PP796 is an inhibitor of phosphodiesterase.

The hypothesis then is that the emesis is mediated by central stimulation of a parasympathetically innervated vomiting centre, probably in the medulla. It is direct and centrally mediated. Parasympathetic stimulation occurs as a reflex response to a very rapid increase in the circulating level of cyclic AMP.



4.2 EMETIC DOSE RESPONSE (DOG)

See report CTL/T/2459

IMPERIAL CHEMICAL INDUSTRIES PLC
CENTRAL TOXICOLOGY LABORATORY
ALDERLEY PARK MACCLESFIELD CHESHIRE UK

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Approved for Issue:

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Date of Issue: -6 MAR 1986

IMPERIAL CHEMICAL INDUSTRIES PLC
CENTRAL TOXICOLOGY LABORATORY
ALDERLEY PARK MACCLESFIELD CHESHIRE UK

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SUMMARY

PP796: EMETIC DOSE RESPONSE STUDY IN DOGS

by

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PP796: EMETIC DOSE RESPONSE STUDY IN DOGS

We, the undersigned, declare that this report constitutes a true record of the actions undertaken and the results obtained in the above study.

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CTL/T/2459

PP796: EMETIC DOSE RESPONSE STUDY IN DOGS

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PP796: EMETIC DOSE RESPONSE STUDY IN DOGS

SUMMARY

The purpose of this study was two-fold: (1) to investigate the emetic response of dogs to different dose levels of PP796, in terms of onset, duration and productivity of vomiting. (2) to assess the acute toxicity following a single oral dose of PP796.

Seven male and 7 female beagle dogs were allocated to treatment groups which received a single dose of PP796 at one of the following dose levels: 0, 0.1, 0.5, 1.0, 3.0, 10.0 or 20.0mg/kg. Clinical observations, food consumption and faecal consistency were recorded daily during a 7 day observation period and the dogs were weighed and examined periodically during this time.

Emesis, with subdued behaviour, was produced at dose levels in the range of 0.5mg PP796/kg to 20mg PP796/kg, no effects occurring at 0 and 0.1mg PP796/kg. The onset of vomiting, the duration and the severity of effects were dose related. Vomiting was more rapid at 10 or 20mg PP796/kg (within 5 mins of dosing) and the effects were more severe than at 3 or 0.5mg PP796/kg. Severe vomiting was present at dose levels of 3mg PP796/kg and above. Diarrhoea and defaecation of mucus were present in some dogs at dose levels of 1.0mg PP796/kg and above. By 6 hours all dogs had recovered.

No other treatment related effects were observed.

0.5mg PP796/kg was considered to represent the minimal effective dose level and 20mg PP796/kg to be the maximum tolerated dose level (based on the severity of effects). The time to vomiting was reduced to within 10 minutes of dosing by increasing the dose to 3mg PP796/kg and to within 5 minutes of dosing by dosing 10 or 20mg PP796/kg. The shortening in the time to initiation of vomiting was associated with an increase in the severity of the effects seen at these dose levels.

1. INTRODUCTION

PP796 is a centrally acting emetic which is included in paraquat formulations in order to induce emesis, and hence reduce absorption of paraquat, should ingestion of the formulation occur. PP796 has been shown to induce vomiting in dogs within 7 minutes, when administered orally at a dose level of 3mg/kg (1).

The purpose of this study was to investigate the response of dogs to different dose levels of PP796, in terms of onset, duration and productivity of vomiting, and to assess the acute toxicity following a single oral dose of PP796.

Dose levels were selected to provide a range from the probable human dose in 10-15ml pesticide formulation (0.05-0.1mg PP796/kg approximately) to approximately 10 times the effective dose in dogs (2-3mg PP796/kg), ie up to 20mg PP796/kg. The species and strain were chosen on the basis of background toxicology data in this Laboratory and because the dog is a vomiting species. The oral route of exposure was selected as this is the likely route in humans and gavage administration was chosen because this was used in previous studies with PP796 in dogs.

The study commenced on 7th August 1985 and was completed on 14th August 1985.

2. MATERIALS AND METHODS

2.1 Test Compound

PP796 (2-amino-6-methyl-4-propyl-4H-1,2,4-triazolo(2,3-A)pyrimidin-5-one), CTL reference number Y00706/016/001, was supplied by Imperial Chemical Industries PLC, Plant Protection Division, Fernhurst, UK, as the technical

paste and aqueous solutions were prepared by Central Dispensary, correcting for purity (82.1%), to give the following dose levels:

| Concentration of PP796 Solution | Dose Volume (ml/kg) | Dose Level (mg PP796/kg) |
|------------------------------------|------------------------|-----------------------------|
| 0.02% | 0.5 | 0.1 |
| 0.1% | 0.5 | 0.5 |
| 0.2% | 0.5 | 1.0 |
| 0.6% | 0.5 | 3.0 |
| 1.0% | 1.0 | 10.0 |
| 1.0% | 2.0 | 20.0 |

Doses were calculated to the nearest 0.1kg bodyweight and were administered via syringes filled manually to the nearest 0.1ml.

2.2 Animals and Accommodation

Seven male and 7 female beagle dogs, approximately 5 months old and from separate litters, were used in this study. They were obtained from the Alderley Park Dog Breeding Unit and acclimatised to the Central Toxicology Laboratory (CTL) environment for 6-7 weeks prior to dosing. They were identified by tattooed ear numbers and, whilst at the Breeding Unit, had received vaccinations against canine distemper, leptospirosis, canine viral hepatitis and parvovirus, and treatments for possible ear mite and nematode infestations.

The dogs were housed individually in the CTL doghouse and were fed 350g LABORATORY DIET A (Special Diets Services Ltd, Stepfield, Witham, Essex, UK) daily. Water was provided ad libitum except on the day of dosing, and the environmental temperature ranged between 19-22°C during the course of the study.

2.3 Experimental Details

The dogs were randomly allocated to treatment groups and assigned experimental numbers:

| Treatment Groups | Treatment (mg PP796/kg) | Animal Identification | | | |
|------------------|-------------------------|-----------------------|------------|------------|------------|
| | | Male | | Female | |
| | | Ear Number | Exp Number | Ear Number | Exp Number |
| 1 | 0 | 165/85 | 1 | 174/85 | 2 |
| 2 | 0.1 | 189/85 | 3 | 193/85 | 4 |
| 3 | 0.5 | 177/85 | 5 | 187/85 | 6 |
| 4 | 1.0 | 166/85 | 7 | 181/85 | 8 |
| 5 | 3.0 | 182/85 | 9 | 194/85 | 10 |
| 6 | 10.0 | 179/85 | 11 | 186/85 | 12 |
| 7 | 20.0 | 166/85 | 13 | 219/85 | 14 |

On the day of dosing (day 1), each dog received 6g of COMPLAN (Farley Health Products Ltd, Plymouth, UK), as 50ml aqueous suspension, by gavage (24FG, Warne Surgical Products) approximately 24hrs after the last normal feed. Immediately afterwards, the test solution was administered via the tube followed by 10ml water. Control dogs received COMPLAN only. Food and water were then withheld until 5-6 hours after dosing. At the end of the 7 day observation period, all dogs were returned to stock.

2.4 Clinical Investigations

2.4.1 Clinical Examinations/Observations: Each dog was given a detailed clinical examination, including cardiac and pulmonary auscultation, prestudy and then on days 1 and 7. Clinical observations were made 2 or 3 times daily; on the day of dosing, each dog was observed continuously for the immediate 2 hour post-dose period and then regularly during the remainder of the day.

Faecal consistency was recorded twice daily during the 7 day observation period.

2.4.2 Bodyweights: Each dog was weighed, prior to feeding, on day -1, day 3 and day 7. The weights recorded on day -1 were used to calculate dosage.

2.4.3 Food Consumption: 24 hour food residues were measured daily during the 7 day observation period, just prior to feeding.

3. RESULTS

3.1 Clinical Examinations/Observations (Table 1)

Individual clinical findings seen after dosing on day 1 are summarised in Table 1. No effects were seen at dose levels of 0 or 0.1mg PP796/kg. Dose levels of 0.5, 1.0, 3.0, 10.0 and 20.0mg PP796/kg caused emesis in a dose-related manner in terms of onset, duration and severity.

Dose levels of 0.5 and 1.0mg PP796/kg produced emesis within 12-30 mins of dosing. The effects seen at these dose levels were of a mild to moderate nature and the dogs had recovered within 1hr-1½hrs after dosing, although vomiting occurred again 2-3½hrs after dosing in two of these dogs (male 5, 0.5mg PP796/kg and female 8, 1.0mg PP796/kg).

Dose levels of 3.0, 10.0 and 20.0mg PP796/kg caused a prompt emetic response; 7-8 mins after dosing at 3.0mg PP796/kg and 5 mins after dosing at 10 or 20mg PP796/kg. The severity and duration of effects was much greater at these dose levels; severe vomiting characterised by prolonged periods of marked retching, diarrhoea, subdued and restless behaviour were seen in most of these dogs. Although vomiting had, in most cases, ceased within 1 hour of dosing, the dogs had not fully recovered until later in the day (generally 2-3hrs after dosing). The female dog dosed with 20mg PP796/kg was more severely affected than any other dog and was still subdued, salivating excessively and had a subnormal temperature 5hrs after dosing, but had improved by 6 hours.

Slight lung sounds were heard on the right side of the thorax of male 13 (20mg/kg PP796) approximately 4hrs after dosing.

Several treated dogs had diarrhoea on day 1 after dosing (females 8 and 10, male 11, and female 14). Other faecal abnormalities seen during the remainder of the observation period were isolated, spread across the treatment groups and considered to be incidental to treatment:

| | | |
|----------|------------------|---|
| Male 1 | (0mg PP796/kg) | - Mucus and blood on day 3 Fluid faeces on day 7 |
| Female 6 | (0.5mg PP796/kg) | - Fluid faeces on day 3 |
| Male 9 | (3.0mg PP796/kg) | - Blood on day 7 |
| Male 13 | (20mg PP796/kg) | - Fluid faeces on day 6 |

No other treatment related effects were observed.

3.2 Bodyweights

Individual bodyweights are presented in Table 2.

There were no treatment related bodyweight effects.

3.3 Food Consumption

Food consumption was 100% at all times in all dogs.

4. DISCUSSION

PP796, when dosed orally to dogs, caused emesis at dose levels in the range of 0.5mg/kg to 20mg/kg. The onset of vomiting was dose related being slowest at 0.5mg PP796/kg (25-27 mins after dosing) and most rapid at 10 and 20mg PP796/kg (5 mins in each case). The severity of effects was also dose-related and severe vomiting was seen at dose levels of 3mg PP796/kg and above. The female dog dosed with 20mg PP796/kg was more severely affected than any other dog and did not fully recover until 6hrs after dosing.

Apart from the immediate effects of PP796 on the gastrointestinal tract there were no other adverse effects of treatment with PP796. It is considered that 0.5mg PP796/kg represents the minimal effective dose level and 20mg PP796/kg the maximum tolerated dose level (based on the severity of vomiting). The time to vomiting is reduced to within 10 minutes of dosing by increasing the dose to 3.0mg PP796/kg, and to within 5 minutes of dosing by increasing the dose to 10 or 20mg PP796/kg. The reduction in the time to initiation of vomiting is associated with an increased severity of clinical effects at these dose levels.

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REFERENCE

- (1) Brammer A and Robinson M (1985). PP796 and TKPP: Acute Toxicity Studies in Dogs. Imperial Chemical Industries PLC, Central Toxicology Laboratory Report No CTL/T/2451.

PP796: Emetic Dose Response Study in Dogs

TABLE 1

SUMMARY OF INDIVIDUAL CLINICAL OBSERVATIONS ON DAY 1

| Treatment (mg/kg PP796) | Animal Number | Clinical Effects (Presence/Incidence) | | | | | | | | | | Eating Vomit | Time to First Vomiting | Approximate Duration of Initial Effects | Approximate Time to Last Vomit |
|----------------------------|------------------|---------------------------------------|----|---|---|----|-----|------|-----|---|-----|-----------------|------------------------------|---|--------------------------------------|
| | | V | LL | S | R | MR | Sub | Rest | Rec | D | Muc | | | | |
| 0 | M 1 | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| | F 2 | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 0.1 | M 3 | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| | F 4 | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 0.5 | M 5 | 2 | - | - | - | - | ✓ | ✓ | - | - | - | ✓ | 25mins | 1hr | 2-3½hrs |
| | F 6 | 4 | - | - | ✓ | - | ✓ | ✓ | ✓ | - | - | - | 27mins | 1hr | 44mins |
| 1.0 | M 7 | 6 | - | ✓ | - | - | - | - | - | - | - | - | 12mins | 1hr | 40mins |
| | F 8 | 9 | - | - | ✓ | - | ✓ | - | - | ✓ | - | - | 20mins | 1hr 20mins | 2-3½hrs |
| 3.0 | M 9 | 5 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | - | - | ✓ | - | 8mins | 1hr | 26mins |
| | F 10 | 11 | - | - | - | ✓ | ✓ | - | ✓ | ✓ | - | ✓ | 7mins | 2-3hrs | 43mins |
| 10.0 | M 11 | 5 | - | - | - | ✓ | ✓ | ✓ | - | ✓ | ✓ | - | 5mins | 42mins | 2½hrs |
| | F 12 | 7 | - | - | ✓ | ✓ | ✓ | ✓ | - | - | - | ✓ | 5mins | 1½-2½hrs | 50mins |
| 20.0 | M 13 | 12 | - | - | - | ✓ | ✓ | - | ✓ | - | - | - | 5mins | 2hrs | 34mins |
| | F 14 | 11 | - | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | - | - | 5mins | 4-6hrs | 1 hrs |

Key: V = vomiting (number of times)
MR = marked retching
D = diarrhoea

LL = licking lips
Sub = subdued behaviour
Muc = mucus per anus

S = excess salivation
Rest = restlessness
✓ = present

R = retching
Rec = recumbency
- = not seen

PP796: EMETIC DOSE RESPONSE STUDY IN DOGS

TABLE 2

BODYWEIGHTS

| Treatment (mg PP796/kg) | Animal Number | Duration | | |
|----------------------------|---------------|----------|-------|-------|
| | | Day -1 | Day 3 | Day 7 |
| 0 | Male 1 | 12.0 | 12.0 | 12.1 |
| | Female 2 | 9.5 | 9.8 | 9.7 |
| 0.1 | Male 3 | 12.3 | 12.5 | 12.5 |
| | Female 4 | 10.7 | 10.9 | 11.0 |
| 0.5 | Male 5 | 12.1 | 12.1 | 12.1 |
| | Female 6 | 10.3 | 10.4 | 10.6 |
| 1.0 | Male 7 | 12.0 | 12.3 | 12.3 |
| | Female 8 | 10.1 | 10.2 | 10.3 |
| 3.0 | Male 9 | 10.9 | 11.1 | 11.2 |
| | Female 10 | 11.6 | 11.5 | 11.8 |
| 10.0 | Male 11 | 11.8 | 11.9 | 11.8 |
| | Female 12 | 10.8 | 10.8 | 10.8 |
| 20.0 | Male 13 | 12.9 | 13.0 | 13.0 |
| | Female 14 | 11.4 | 11.4 | 11.6 |

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REPORT NO: CTL/T/2471

SUMMARY

PP796: EMETIC STUDY IN PARAQUAT
TREATED DOGS

by

M Robinson
A Brammer

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PP796: EMETIC STUDY IN PARAQUAT TREATED DOGS

We, the undersigned, declare that this report constitutes a true record of the actions undertaken and the results obtained in the above study..

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PP796: EMETIC STUDY IN PARAQUAT TREATED DOGS

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PP796: EMETIC STUDY IN PARAQUAT TREATED DOGS

SUMMARY

A previous study showed that different doses of the emetic PP796 in dogs induced different times to initiation of vomiting and different degrees of emetic response. This study was performed in order to investigate the effects, in dogs, of different doses of PP796 when administered simultaneously with paraquat.

Groups of 3 male dogs were dosed orally with 20mg/kg paraquat ion (as the dichloride) and with 0, 0.5, 3.0 or 20mg/kg of the emetic PP796.

The effects of paraquat administration were assessed in the 4 groups by: i) peak plasma paraquat concentration, ii) area under the plasma paraquat concentration/time curve and iii) grossly observable paraquat-related lung lesions at necropsy 8 days after dosing.

There was a marked decrease in the peak plasma paraquat concentration, area under the curve and the severity of the paraquat-related lung lesions of dogs dosed with 0.5mg/kg or 3.0mg/kg PP796 + paraquat when compared with dogs dosed with paraquat alone. These reductions were dose related. The response in dogs dosed with 20mg/kg PP796 + paraquat was variable, some dogs showing a reduction in the effects of paraquat whilst others showed no decrease. One dog showed evidence of increased effects of paraquat which were considered to be probably due to increased paraquat absorption resulting from regurgitation and inhalation of part of the gavage dose.

It is considered that the effective dose range of the emetic PP796, in dogs, in terms of reducing the absorption and effects of paraquat is between 0.5mg/kg and 3.0mg/kg. High doses of PP796 provide no advantages over a dose of 3.0mg/kg and may, in some dogs, be contra-indicated.

1. INTRODUCTION

PP796 is an emetic which is believed to act centrally via the chemoreceptor trigger zone and is currently incorporated into some paraquat formulations in order to reduce toxicity in humans should ingestion occur. The simultaneous administration of paraquat and an emetic dose of PP796, to dogs, resulted in lowered plasma concentrations of paraquat ion and reduced signs of toxicity when compared with dogs dosed with paraquat alone (1). Different dose levels of PP796 have been shown to elicit different degrees of emetic response in dogs (2).

The purpose of this study was to investigate the effects of different dose levels of PP796 on the plasma profile and toxicity of paraquat in dogs, in order to select a concentration of PP796 for paraquat formulations which may provide optimum protection for humans.

The dose levels of PP796 used in this study (0.5, 3 and 20mg/kg) were selected on the basis of previous work in dogs where 20mg/kg was considered to be the maximum tolerated dose level (2). The dose level of 20mg paraquat ion/kg was chosen since this was considered to be a non-lethal dose which would provide measurable levels of paraquat ion in plasma.

The study commenced on 17th September 1985 and the in-vivo phase was completed on 26th September 1985.

2. MATERIALS AND METHODS

2.1 Test Compounds and Dose Preparation

2.1.1 PP796: PP796 (Y00706/016/002) was supplied as the technical paste by ICI PLC, Plant Protection Division, Fernhurst, Surrey, and prepared as aqueous solutions, correcting for purity (82.1%), by Central Dispensary as follows:

0.1% solution dosed at 0.5ml/kg = 0.5mg/kg
0.6% solution dosed at 0.5ml/kg = 3.0mg/kg
1% solution dosed at 2ml/kg = 20.0mg/kg

2.1.2 Paraquat: Paraquat dichloride (Y00061/066/001) was supplied by Mond Division as the technical liquor containing 33.07% paraquat ion. An aqueous 8% paraquat ion solution was prepared by the Central Dispensary, Central Toxicology Laboratory (CTL), and dosed at 0.25ml/kg bodyweight to give a dose level of 20mg paraquat^{*} ion/kg bodyweight.

Doses were calculated to the nearest 0.1kg and the appropriate volume of each test solution was check-weighed into syringes for administration via gavage. (A density of 1.0 was assumed for the prepared dosing solutions).

2.2 Animals and Accommodation

Thirteen male beagle dogs from separate litters, were used in this study and were 24-30 weeks old when dosed. They were obtained from the Alderley Park Dog Breeding Unit and were acclimatised to the CTL environment for at least 1 week prior to treatment. Whilst at the Breeding Unit they had received vaccinations against canine distemper, leptospirosis, canine viral hepatitis and parvovirus and treatment for possible ear mite and nematode infestations. The dogs were identified by tattooed ear numbers which were cross-referenced to experimental numbers following randomisation.

The dogs were housed in the CTL dog house and were fed 350g Laboratory Diet A (Special Diet Services Ltd, Stepfield, Witham, Essex) daily. Water was provided ad libitum except on the day of dosing. The environmental temperature ranged between 19-23°C during the course of the study.

^{*}Subsequently, in this report, 'paraquat' refers to 20mg paraquat ion/kg bodyweight.

2.3 Experimental Design

Initially twelve dogs were used in this study but because of the effects seen in one group 4 dog (male 10) after dosing on day 1, another dog (male 13) was introduced to this group.

Dogs were assigned to treatment groups as follows:

| Group | Treatment | Experimental Numbers |
|----------------|---------------------------------------|----------------------|
| 1 (control) | 20mg paraquat ion/kg | 1 - 3 |
| 2 | 20mg paraquat ion/kg + 0.5mg PP796/kg | 4 - 6 |
| 3 | 20mg paraquat ion/kg + 3 mg PP796/kg | 7 - 9 |
| 4 | 20mg paraquat ion/kg + 20 mg PP796/kg | 10 - 13 |

On the day of dosing (day 1), each dog received 6g COMPLAN (Farley Health Products Ltd, Plymouth) as a 50ml aqueous suspension, by gavage (24FG, Warne Surgical Products), approximately 24 hours after the last normal feed. Immediately afterwards the appropriate volume of test solution(s) was administered via the gavage tube followed by 10ml water. Food and water were then withheld for 6 hours after dosing.

Dogs 1-12 were dosed on 17th September 1985 and dog 13 was dosed on 19th September 1985. Each dog was observed for 7 days and killed on day 8.

2.4 Clinical Investigations

The dogs were observed, continuously for the first 1-2½ hrs after dosing and then frequently during each working day, for gross clinical or behavioural abnormalities. Clinical examinations, including cardiac and pulmonary auscultation, were made pre-study, on day 1 (5-8 hrs after dosing) and terminally.

2.5 Plasma Paraquat Concentrations

2ml blood samples were obtained from each dog at the following scheduled time points: pre-dose, 5, 15 and 30 mins, 1, 2, 3, 4, 6, 8, 12, 24, 48 and 72 hours post-dose and placed in tubes containing lithium/heparin anticoagulant. The plasma was stored at -20°C prior to analysis of the paraquat concentration by radioimmunoassay.

The sampling times were noted (particularly during the first hour) so that the plasma levels could be plotted accurately.

The area under the plasma concentration, versus time curve (AUC), for the initial 24 hour post-dose period, was calculated by the trapezoidal rule (3).

2.6 Terminal Procedures

At termination (day 8) all surviving dogs were killed by deep pento-barbitone anaesthesia (EUTHATAL, May and Baker Ltd, Dagenham, Essex) and exsanguination. Gross necropsies were performed and the following tissues were removed and fixed:-

Adrenal gland, kidney, liver, lung, stomach, any abnormal tissue.

Tissues were fixed in 10% neutral buffered formol saline and stored.

One dog (male 10, 20mg/kg PP796 + paraquat) was killed on day 4 due to adverse clinical signs and necropsied as above. In addition fixed portions of lung from this dog were processed for histology, paraffin wax embedded and 5µm sections were cut and stained with haematoxylin and eosin. Sections were examined by light microscopy.

2.7 Statistical Analysis

The following data were subjected to statistical analyses:

- 1) time to first vomit
- 2) peak plasma level

- 3) AUC
- 4) qualitative assessment of lung lesion

Where appropriate, the data were considered using analysis of variance and intergroup comparisons were made on the basis of a Student's t-test following a log transformation. A higher level of variation was noted between dogs in Group 4 with regard to all 4 variables. This precluded using the analysis of variance approach into differences in mean value between this group and the other 3 groups for peak plasma level and area under curve for this group. The Mann-Witney U-test was used to compare the assessed lung lesions (4).

3. RESULTS

Peak plasma levels, AUC, time to first vomiting and lung lesion assessments are presented, for each animal, in Table 1. Group means and the results of statistical analyses are presented in Table 2 (except lung lesion assessments).

3.1 Mortalities

Male 10, Group 4 (20mg/kg PP796 + paraquat) was killed on day 4 due to adverse clinical signs.

There were no other mortalities and all other dogs, including those dosed with paraquat alone, remained in good general clinical condition during the 7 day observation period.

3.2 Clinical Observations (Tables 1 and 2, Appendix 1)

Clinical findings are summarised for each animal in Appendix 1.

All dogs dosed with PP796 showed a decreased time to first vomit after dosing when compared with those dosed with paraquat alone (group 1). Dogs dosed with 20mg/kg PP796 + paraquat showed a shorter mean time to

first vomit than those dosed with 3mg/kg PP796 + paraquat and both of these groups showed a shorter mean time to first vomit than dogs dosed with 0.5mg/kg PP796 + paraquat (although only the difference between 20mg/kg and 0.5mg/kg PP796 + paraquat attained statistical significance).

Clinical signs were severe in those dogs dosed with 20mg/kg PP796 + paraquat. Vomiting was accompanied by prolonged episodes of marked retching and subdued behaviour, restlessness and recumbency, and these effects lasted for about 5 hours after dosing. One dog in this group (male 10) struggled violently during the dosing procedure and vomited soon after dosing (1½ minutes). Laboured, rapid respiration became evident 30 minutes after dosing. Although this improved over the next 24 hours, by day 4 the dog had a slightly productive cough, increased respiratory sounds in the lungs and upper respiratory tract, appeared slightly dehydrated and was subdued. It was killed on day 4 for humane reasons.

At 3mg/kg PP796 + paraquat, subdued behaviour, recumbency and panting accompanied vomiting but these effects were apparent only during the initial 1-2 hours post dosing.

0.5mg/kg PP796 + paraquat produced mild clinical effects. Slight hypoactivity was apparent in the first 1-2½ hours and vomiting occurred in the first hour after dosing.

Paraquat alone (20mg/kg) was tolerated well. Slight hypoactivity was seen within the first 1½ hours of dosing and the time to vomiting was extremely variable (1 hour 15 mins for male 1, 29 hours for male 2). Male 3 showed the most severe effects (vomiting occasionally over 4 days and leaving food).

3.3 Plasma Paraquat Concentrations (Tables 1 and 2, Figure 1, Appendix 2)

The peak plasma paraquat levels of dogs dosed with 0.5 or 3.0mg/kg PP796 + paraquat were markedly lower than those of dogs dosed with paraquat alone (approximately 10-fold). There was some evidence,

supported statistically, that values in dogs dosed with 3.0mg/kg PP796 + paraquat were lower than in dogs dosed with 0.5mg/kg PP796 + paraquat. The values in dogs dosed with 20mg PP796 + paraquat, with the exception of male 10, were lower than in dogs dosed with paraquat alone. However the variability in this group precluded useful statistical comparison with values in groups 2 and 3.

The AUCs of dogs dosed with 0.5 or 3.0mg/kg PP796 + paraquat were also markedly lower than those of dogs dosed with paraquat alone (approximately 10-fold). There was some evidence, supported statistically, that values in dogs dosed with 3.0mg/kg PP796 + paraquat were lower than in dogs dosed with 0.5mg/kg PP796 + paraquat. The values in dogs dosed with 20mg/kg PP796 + paraquat, with the exception of male 10, were lower than in dogs dosed with paraquat alone. Statistical analysis of these data was not performed due to the greater variability in this group.

3.4 Pathology (Table 3, Appendix 3)

A number of treated dogs showed gross lung lesions which were considered to be related to paraquat toxicity. These lesions took the form of dark red areas, some of which were consolidated.

There was a decrease, supported statistically, in the severity of the lung lesion in dogs dosed with 0.5 and 3.0mg/kg PP796 + paraquat when compared with dogs dosed with paraquat alone. There was no statistical evidence for any difference in the severity of paraquat related lung lesions in dogs dosed with 3.0mg/kg PP796 + paraquat (group 3) when compared to those dosed with 0.5mg/kg PP796 + paraquat (group 2). However, 1 dog in group 2 showed minimal change whereas no paraquat-related lesions were present in group 3.

There was considerable variation in the severity of paraquat-related lung lesions in dogs dosed with 20mg/kg PP796 + paraquat. Paraquat-related lesions were absent in male 12 whereas the lungs of male 10 (killed prematurely) showed marked changes. Overall these lesions approached the severity of those present in dogs dosed with paraquat alone and were, generally, more severe than those present in group 2 and 3.

Other gross lesions were considered not to be treatment related.

Histopathology: There was a moderate pneumonitis in the lung of dog 10. This lesion was composed of alveolar inflammatory cells, interalveolar and peribronchiolar fibrosis and focal epithelialisation. In addition, there were areas of alveolar haemorrhage and focal emphysema. One bronchus contained strands of basophilic material mixed with inflammatory cells.

4. DISCUSSION

The effects of orally administered paraquat and different dose levels of PP796, in dogs, were compared with the effects of paraquat alone by the assessment of 3 variables: 1) peak plasma concentration

2) AUC

3) qualitative assessment of lung
lesion

For each of these assessments, there was strong evidence that 0.5 and 3.0mg/kg PP796 reduced the effects of paraquat when compared with dogs dosed with paraquat alone. There was also some evidence that 3.0mg/kg PP796 induced a greater reduction in the effects of paraquat than 0.5mg/kg PP796.

It is clear that dogs dosed with 20mg/kg PP796 showed a markedly variable response to the effects of paraquat administration. In particular, the results obtained from dog 10 were abnormal for the group as a whole. The clinical signs of rapid, laboured respiration were of much greater severity and duration than those seen in any other dog in the study. Also, the peak plasma concentration and area under the curve were markedly elevated above the values of other dogs in this group and, indeed, were considerably higher than values in dogs treated with paraquat alone. In addition, the lung lesions present in dog 10 were similar to the most severely affected dog in the paraquat-alone group. The plasma paraquat profile of dog 10 indicated that an abnormally high proportion of the

administered dose of paraquat had been absorbed. The reason for these results in dog 10 is uncertain. There was no pathological evidence for tracheal damage or lung dosing. However the strands of basophilic material seen in the lungs on histology may indicate that some inhalation of some regurgitated stomach contents had occurred. Since the paraquat was administered separately from the COMPLAN at dosing, the abnormally high plasma paraquat values and the absence of an inhalation pneumonia may be explained by regurgitation and inhalation of the paraquat/PP796 dose and stomach retention of the COMPLAN during dosing. The difficulty experienced in dosing this animal because of marked struggling may have enabled this differential regurgitation of the total gavage dose to have occurred.

Whilst the results obtained in dog 10 may be explained on the above basis, the results obtained in dog 11 also indicate a lesser reduction of the effects of paraquat than dogs 12 and 13. The peak plasma paraquat level was similar to the highest value in dogs dosed at 0.5mg/kg PP796 + paraquat, the AUC was considerably higher than in dogs 12 and 13 and the lung lesions were more severe than any other dog dosed with PP796 (with the exception of dog 10). This lessening in the reduction of effects of paraquat was present in spite of a very short time to first vomit. Thus although 20mg/kg PP796 produced a greater reduction in the effects of paraquat, in some dogs, when compared with 0.5mg/kg or 3.0mg/kg, dog 11 showed a reversal of this trend. There are several possible explanations for this reversed trend:

- (a) excessive and violent retching and vomiting may induce inhalation of some of the administered gavage dose;
- (b) excessive and violent retching and vomiting may cause minor damage to the gastric mucosa allowing enhanced absorption of paraquat;
- (c) high doses of PP796 cause not only a decreased time to first vomiting and increased vomiting but also increased gastric emptying via the pylorus.

The absence of gastric haemorrhage either clinically or at necropsy in this study indicates that significant gastric damage was not present. Also, the low pH of the stomach contents is likely to preclude significant paraquat absorption. Dogs treated with 20mg/kg PP796 showed, clinically, increased intestinal motility by virtue of the production of liquid or mucoid faeces after dosing although it is not known if this increased motility included gastric emptying into the duodenum. Evidence of inhalation of regurgitated material was present in dog 10 (the presence of basophilic material in lung histology and exceptionally high plasma paraquat levels) and it is considered that this event is the most likely explanation of the reversal of beneficial effects of PP796 when given at high doses.

The time to initiation of vomiting was progressively reduced following PP796 administration, in a dose-related manner, as reported previously (2). However the results of this study indicate that this variable alone cannot be used to assess the possible consequences of paraquat administration.

5. CONCLUSION

The emetic PP796 reduced the effects of paraquat when administered simultaneously. This agrees with previous findings (1).

In this study, increased doses of PP796 progressively reduced the effects of oral paraquat administration up to a maximum dose of 3.0mg/kg PP796.

Large doses of PP796 (20mg/kg) resulted in a marked variability in the effects of paraquat, some dogs showing further reductions in the effects of paraquat whilst others showed a reversal of this trend.

Doses of the emetic PP796 in the order of 0.5mg/kg or 3.0mg/kg are clearly beneficial in the reduction of the effects of oral paraquat administration in dogs. Large doses of PP796 eg 20mg/kg provide no additional benefit over 0.5mg/kg and 3.0mg/kg and may in some individual animals be contra-indicated.

REFERENCES

1. Rose M S (1976). The effect of administration of an emetic (PP796) on paraquat toxicity in the dog and monkey. CTL Report No CTL/R/391.
2. Brammer A and Robinson M (1985). PP796: Emetic dose response study in dogs. CTL Report No CTL/T/2459.
3. Notari R E (1980). In 'Biopharmaceutics and Clinical Pharmacokinetics. An Introduction. Marcel Dekker Inc., New York, USA. 3rd Ed pp 86-87.
4. Mann H B and Whitney D R (1947). On a test of whether one of two random variables is stochastically larger than the others. Annals of Mathematical Statistics 18.

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20.12.85

PP796: EMETIC STUDY IN PARAQUAT TREATED DOGS

TABLE 1

SUMMARY OF RESULTS

| Treatment Group | Dog No. | Peak Plasma Level (µg/ml) | AUC (0-24hrs) | Time to First Vomit | Lung Lesion (Dark red area) |
|-----------------------------------|---------|---------------------------|-----------------------|---------------------|-----------------------------|
| 1 Paraquat | 1 | 8.88 | 26.838 | 1hr 15 mins | Moderate |
| | 2 | 12.50 | 32.368 | 29hr | Slight |
| | 3 | 7.62 ⁽¹⁾ | 48.327 ⁽¹⁾ | 6hr | Marked |
| 2 Paraquat + 0.5mg/kg PP796 | 4 | 0.72 ⁽²⁾ | 2.865 ⁽²⁾ | 24mins | NAD |
| | 5 | 1.43 | 4.326 | 8mins | Minimal |
| | 6 | 0.83 | 3.012 | 26mins | NAD |
| 3 Paraquat + 3.0mg/kg PP796 | 7 | 0.12 | 0.465 | 6mins | NAD |
| | 8 | 0.58 | 1.654 | 5½mins | NAD |
| | 9 | 0.37 | 1.176 | 4mins | NAD |
| 4 Paraquat + 20mg/kg PP796 | 10 | 26.70 | 52.964 | 1½mins | Marked |
| | 11 | 1.42 | 2.478 | 3mins | Slight |
| | 12 | 0.11 | 0.390 | 6mins | NAD |
| | 13 | 0.10 | 0.460 | 3mins | Minimal |

(1) excluding 8 hour results (0.04µg/ml).

(2) excluding 8 hour results (1.52 µg/ml).

PP796: EMETIC STUDY IN PARAQUAT TREATED DOGS

TABLE 2

STATISTICAL ANALYSIS OF GROUP MEAN DATA

| Group and Treatment | Time to First Vomit (minutes) (Log transformed data) | | Area Under Curve (Log transformed data) | | Peak Plasma Level (µg/ml) (Log transformed data) | |
|---|---|------|--|-------------------|--|-------------------|
| | Transformed Mean | Mean | Transformed Mean | Mean | Transformed Mean | Mean |
| 1 Paraquat | 2.56 A | 725 | 1.541 A | 35.8 | 0.976 A | 9.67 |
| 2 0.5mg/kg PP796 + paraquat | 1.23 B | 19 | 0.524 B | 3.4 | -0.023 B | 0.99 |
| 3 3.0mg/kg PP796 + paraquat | 0.71 BC | 5 | -0.015 C | 1.1 | -0.530 C | 0.36 |
| 4 20.0mg/kg PP796 + paraquat | 0.48 C | 3 | - | 14.1 [†] | - | 7.08 [†] |
| Least Significant Difference [‡] (LSD) p = 0.05 | 0.70 | | 0.379 | | 0.463 | |

The outcomes of the individual intergroup comparisons using Student's t-test are annotated by the letters which accompany group means. Treatments with no letters in common are significantly different at the 5% level.

‡ This represents the between-group difference required to achieve Statistical Significance at 5%.

† Group 4 not included in Statistical Analysis due to the high level of variability

PP796: EMETIC STUDY IN PARAQUAT TREATED DOGS

TABLE 3

INCIDENCE OF GROSS PATHOLOGICAL FINDINGS IN LUNGS

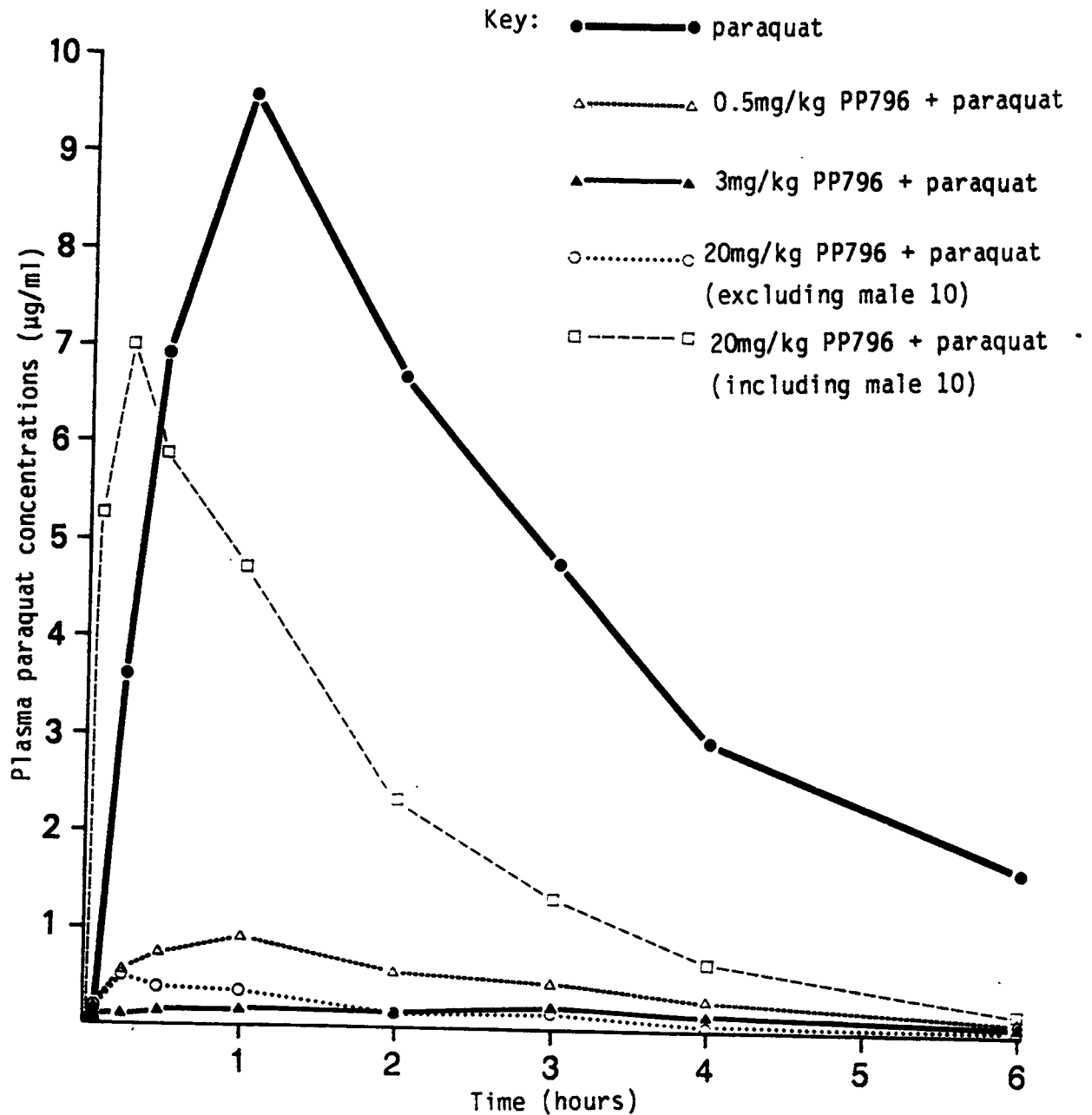
| Gross Lung Observation | Treatment Group | | | |
|----------------------------|-----------------|-------------------------------------|-------------------------------------|------------------------------------|
| | 1 (Paraquat) | 2 (Paraquat + 0.5mg/kg PP796) | 3 (Paraquat + 3.0mg/kg PP796) | 4 (Paraquat + 20mg/kg PP796) |
| Number of Animals Examined | 3 | 3 | 3 | 4 |
| No abnormality detected | 0 | 0 | 1 (9) | 1 (12) |
| Firm nodules | 1 (1) | 2 (4) (6) | 2 (7) (8) | 0 |
| Focal pleural adhesion | 0 | 1 (6) | 0 | 0 |
| Dark red area - minimal | 0 | 1 (5) | 0 | 1 (13) |
| - slight | 1 (2) | 0 | 0 | 1 (11) |
| - moderate | 1 (1) | 0 | 0 | 0 |
| - marked | 1 (3) | 0 | 0 | 1* (10) |

*Intercurrent death () animal number

PP796: EMETIC STUDY IN PARAQUAT TREATED DOGS

FIGURE 1

GROUP MEAN PLASMA PARAQUAT CONCENTRATION/TIME CURVES



Times are approximate up to 1 hour

HAZARD DATA SHEET

This information must not be disclosed outside ICI except with the permission of Organics Division T.L.O.

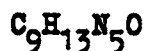
Company Reference
Division Reference HS 1999
Other Reference

**CHEMICAL AND TRADE NAMES****FORMULA**

PP796

Paraquat Emetic

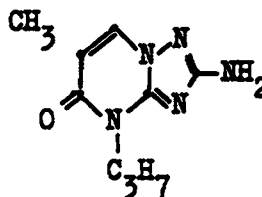
2-Amino-6-methyl-5-oxo-4-propyl-4,5-dihydro-s-triazolo(1,5-a)pyrimidine



Chemical Abstracts Reg. No. 27277-00-5

Reference HS 1999/84

001084

**TOXICITY SUMMARY**

The material is toxic by ingestion, causing rapid respiration, salivation and possibly convulsions. Inhalation of the dust may cause nausea and vomiting. It is a slight irritant to the skin and eyes. On the basis of animal studies, the chronic toxicity will be low.

PRECAUTIONS**Storage**

Store in containers with two plastic liners. Keep containers tightly sealed. Store in a cool place away from contact with sources of ignition.

Plant

Plant should be designed to achieve containment of the material. Ensure good ventilation of working areas, providing draughting/ventilation facilities if necessary to prevent atmospheric contamination. Do not allow the paste to dry out. Protect the dry material from sources of ignition.

Personal Protection

Wear PVC gloves. Wear fresh air breathing apparatus if there is risk of exposure to the dust.

Spills

Clear spillages to containers, seal and remove for recovery or disposal. Decontaminate the affected area by swilling carefully (to avoid dispersion of dust) with plenty of water.

IMMEDIATE TREATMENT**Inhalation**

Remove from exposure. Obtain medical attention if ill-effects result.

Skin Contact

Wash the affected skin with water.

Eye Contact

Irrigate the eye with water. Obtain medical attention if irritation results.

Ingestion

Wash out the mouth with water. Obtain medical attention if ill-effects result.

FURTHER MEDICAL TREATMENT

Symptomatic.

M 2222/s
AJM

| |
|-------------------------|
| PRECAUTIONS |
| RECEIVED 21 NOV 1984 |
| Copy No. |

CHEMICAL AND PHYSICAL PROPERTIES

A white crystalline solid as an aqueous paste or dry powder.

Solubility in water : slightly soluble

Melting point : 165°C

TOXICITY Hygiene Standard (8 hr TWA) 0.1 mg/m³

Acute

Ingestion

Oral LD50 : 150 mg/kg. (2)

Resulted in rapid respiration, salivation and, in some cases, convulsions.

Inhalation

No data. There have been two cases of human exposure. A process operator suffered nausea when handling the material without respiratory protection. A fitter exposed during a plant changeover operation, experienced nausea.

Skin contact

Slight irritant. (2)

Not a strong sensitiser. (3)

Eye contact

Slight irritant. (2)

Chronic

Repeated oral administration to rats (5 mg/day) and dogs (.5mg/day) for 3 months caused no histological changes in any organs. (2)

No teratogenic effects in rabbits or rats (1.25 mg/kg). A 78 week study in mice, dosed at 20 ppm, indicated that the material is not carcinogenic. (2)

LEGISLATION/CODES OF PRACTICE

FIRE AND EXPLOSION

The dry powder may form flammable mixtures with air. The material will be combustible at elevated temperatures, evolving toxic gases. The material may undergo decomposition on strong heating, evolving flammable and toxic gases.

REFERENCES

1. DMD. PP796. Toxicity & Medical Hazards Form, TM88, March 1979.
2. Pharmaceuticals Division. ICI 63197. Safety Evaluation Results 18.7.83.
3. CTL. Paraquat Emetic. Skin Sensitisation. CTL/T/1277

ORIGIN

Organics Division

October, 1984

Subfile = CTL REPORTS , Security = A , Doc Type = BACKLOG

User Ref = 780929 , Acc Date = 25-Jun-86

REPORT NUMBER CTL/C/00575 CATEGORY B

ISSUE DATE 29 SEP 78

TITLE

ATROPINE

FENTAZIN

MAXOLON

PHENERGAN

2-AMINO-4,5-DIHYDRO-6-METHYL-5-OXO-4-PROPYL-S-TRIAZOLO(1,5-A
THE EFFECT OF 4 ANTIEMETIC SUBSTANCES ON THE EMETIC ACTIVITY OF
PP796 IN CYNOMOLGUS MONKEYS

EMETIC RESPONSE

INTRAMUSCULAR

ORAL DOSING

SUBCUTANEOUS

SPONSOR

PPD

DIV REF

CONTRACT LAB. HRC

CONTRACT NO. HRC ICI/193/78628

Y NUMBER

Y00706/000

H NUMBER

H14061

MISC DETAILS MONKEY

Subfile = CTL REPORTS , Security = A , Doc Type = BACKLOG

User Ref = 780928 , Acc Date = 25-Jun-86

REPORT NUMBER CTL/C/00576 CATEGORY B

ISSUE DATE 28 SEP 78

TITLE

2-AMINO-4,5-DIHYDRO-6-METHYL-5-OXO-4-PROPYL-S-TRIAZOLO(1,5-A
THE EFFECTS OF EMETIC PP796 ON THE ORAL TOXICITY OF DIQUAT IN
CYNOMOLGUS MONKEYS

EMETIC RESPONSE

ORAL DOSING

SPONSOR

PPD

DIV REF

CONTRACT LAB. HRC

CONTRACT NO. HRC ICI 172/78481

Y NUMBER

Y00706/000

H NUMBER

H14061

MISC DETAILS MONKEY

Subfile = CTL REPORTS , Security = A , Doc Type = BACKLOG

User Ref = 781108 , Acc Date = 25-Jun-86

REPORT NUMBER CTL/C/00613 CATEGORY B

ISSUE DATE 08 NOV 78

TITLE

2-AMINO-4,5-DIHYDRO-6-METHYL-5-OXO-4-PROPYL-S-TRIAZOLO(1,5-A
THE TOXICITY OF ORALLY ADMINISTERED EMETIC PP796 IN CYNOMOLGUS
MONKEYS

EMETIC RESPONSE

ORAL DOSING

SPONSOR

PPD

DIV REF

CONTRACT LAB. HRC

CONTRACT NO. HRC ICI 171/78627

Y NUMBER

Y00706/000

H NUMBER

H14061

MISC DETAILS MONKEY

Subfile = CTL REPORTS , Security = A , Doc Type = BACKLOG

User Ref = 790319 , Acc Date = 25-Jun-86

REPORT NUMBER CTL/C/00700 CATEGORY B

ISSUE DATE 19 MAR 79

TITLE

GRAMOXONE W

PARAQUAT

2-AMINO-4,5-DIHYDRO-6-METHYL-5-OXO-4-PROPYL-S-TRIAZOLO(1,5-A
THE ACUTE ORAL TOXICITY AND MODE OF ACTION OF EMETIC PP796 IN
CYNOMOLGUS MONKEYS, AND ITS EFFECT UPON THE ACUTE ORAL

EMETIC RESPONSE
ORAL DOSING
RETENTION
SPONSOR PPD DIV REF
CONTRACT LAB. HRC
CONTRACT NO. HRC ICI 119/78556
Y NUMBER

Y00706/000
Y00061/000
H NUMBER H14061
MISC DETAILS MONKEY

Subfile = CTL REPORTS , Security = A , Doc Type = BACKLOG
User Ref = 790621 , Acc Date = 25-Jun-86
REPORT NUMBER CTL/C/00728 CATEGORY B
ISSUE DATE 21 JUN 79
TITLE ETHYLENE GLYCOL
2-AMINO-4,5-DIHYDRO-6-METHYL-5-OXO-4-PROPYL-S-TRIAZOLO(1,5-A
THE EFFECTS OF EMETIC PP796 ON THE ORAL TOXICITY OF ETHYLENE
GLYCOL IN CYNOMOLGUS MONKEYS
EMETIC RESPONSE
ORAL DOSING

SPONSOR PCD DIV REF
CONTRACT LAB. HRC
CONTRACT NO. HRC ICI 292/79470
Y NUMBER Y00836/000
Y00706/001
H NUMBER H00402 H14061
MISC DETAILS MOUSE

Subfile = CTL REPORTS , Security = A , Doc Type = BACKLOG
User Ref = 770916 , Acc Date = 25-Jun-86
REPORT NUMBER CTL/C/00746 CATEGORY B
ISSUE DATE 16 SEP 77
TITLE E605
2-AMINO-4,5-DIHYDRO-6-METHYL-5-OXO-4-PROPYL-S-TRIAZOLO(1,5-A
THE EFFECTS OF EMETIC PP796 ON THE ORAL TOXICITY OF PARATHION IN
CYNOMOLGUS MONKEYS
EMETIC RESPONSE
ORAL LD50
ORAL DOSING

SPONSOR PPD DIV REF
CONTRACT LAB. HRC
Y NUMBER
Y00706/000
H NUMBER H14061
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Subfile = CTL REPORTS , Security = A , Doc Type = BACKLOG
User Ref = 791010 , Acc Date = 25-Jun-86
REPORT NUMBER CTL/C/00775 CATEGORY B
ISSUE DATE 10 OCT 79
TITLE FURADAN
2-AMINO-4,5-DIHYDRO-6-METHYL-5-OXO-4-PROPYL-S-TRIAZOLO(1,5-A
THE EFFECTS OF EMETIC PP796 ON THE ORAL TOXICITY OF FURADAN IN
CYNOMOLGUS MONKEYS
EMETIC RESPONSE
ORAL DOSING

SPONSOR PPD DIV REF
CONTRACT LAB. HRC
CONTRACT NO. HRC ICI 282/79469
Y NUMBER Y00611/000
Y00706/001

Acc Date = 01-Jan-83
Report No PH18987-C Vol II July 1970 I2243P
ICI 63,197 Pharmacology and biochemistry
ICI Pharmaceuticals Division
I2243P
H14061

human papers
database
(2 AT B)

<00>Toxicology

Subfile = REPRINTS , Security = Z , Doc Type = DOCUMENTTYPE66

Acc Date = 01-Jan-83

Report No. PH18987-C I22430 July 1970

Submission of evidence to the committee on safety of drugs prior
to the introduction into humans of ICI 63,197

ICI Pharmaceuticals Division

I22430

H14061

<00>Toxicology

Subfile = REPRINTS , Security = Z , Doc Type = DOCUMENTTYPE66

Acc Date = 01-Jan-83

I2243N

Application to the licensing authority for a clinical trial
certificate in respect of ICI 63,197

ICI Pharmaceuticals Division

I2243N

Skin tox dog skin irritancy, rabbit, guinea pig, skin
sensitisation rabbit

H14061

<00>Toxicology

Subfile = REPRINTS , Security = Z , Doc Type = DOCUMENTTYPE66

Acc Date = 01-Jan-83

I2243M

Application to the licensing authority for the issue of an
animal test certificate in respect of 63,197

ICI Pharmaceuticals Division

I2243M

Acute oral tox rat, acute iv tox mouse rat rabbit
acute im pig

H14061

<00>Toxicology

Subfile = REPRINTS , Security = Z , Doc Type = DOCUMENTTYPE66

Acc Date = 01-Jan-83

Unpublished Report Nov 1978 I2336X

pp 796 added to Gramoxone 1. Effects on acute toxicity in rats 2.
Effects on users 3. effects of various compounds as a possible
antidote in paraquat poisoning

Nihon Nohyaku Co Ltd

I2336X acute occupational oral human spray

H00534, H14061

<00>Toxicology Experimental

Subfile = ABSTRACTS , Security = Z , Doc Type = DOCUMENTTYPE66

Acc Date = 01-Jan-83

ICI Limited Brit Appl 76/15584 p6 1976

Herbicidal composition of bipyridylum quaternary salts
and emetic amounts of s-triazolo pyrimidine derivatives

GE Davies DM Foulkes

Chem Abstr 87(23) 178760 1977

H00534, H14061

<00>Treatment

Subfile = JOURNALS , Security = Z , Doc Type = DOCUMENTTYPE66

Acc Date = 01-Feb-86

VET HUM TOXICOL 27(5) 381-5 1985

EMTIC EFFECT OF TRIAZOLOPYRIMIDINE A PYRIMIDINE COMPOUND IN DOGS

F AKAHORI T ICHIMURA T MASAOKA S ARAI

1985

ACUTE ORAL

H14061

Subfile = SEARCHES , Security = C , Doc Type = DOCUMENTTYPE66

Acc Date = 01-Mar-86

2ND JULY 1976

LITERATURE SEARCH IN CONNECTION WITH TOXICOLOGICAL INQUIRY ON ICI
63,197 FROM PHARMACEUTICALS DIVISION NO INFORMATION FOUND

RB WRIGHT

1976

H14061

Subfile = SEARCHES , Security = C , Doc Type = DOCUMENTTYPE66

Acc Date = 01-Mar-86

2ND JULY 1976

LITERATURE SEARCH IN CONNECTION WITH TOXICOLOGICAL INQUIRY ON ICI
65,329 FROM PHARMACEUTICALS DIVISION NO INFORMATION FOUND

RB WRIGHT

1976

H14061

Subfile = SEARCHES , Security = C , Doc Type = DOCUMENTTYPE44

Acc Date = 06-Oct-89

17 AUGUST 1989 S206J

SENSITIZATION DATA ON ADJUVANTS IN JAPANESE DIQUAT FORMULATIONS

J W BOTHAM

S206J

GUINEA PIG HUMAN RABBIT EYE IRRITATION SENSITISATION SKIN URTICARIA
H00647 H01340 H04737 H36575 H14061 H38122 H16751 H26245

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User Ref = 780929 , Acc Date = 25-Jun-86

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REPORT NUMBER CTL/C/00575 CATEGORY B
ISSUE DATE 29 SEP 78
TITLE

ATROPINE
FENTAZIN
MAXOLON
PHENERGAN
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SPONSOR PPD
CONTRACT LAB. HRC
CONTRACT NO. HRC ICI 172/78481
Y NUMBER Y00706/000
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MISC DETAILS MONKEY

DIV REF

Subfile = CTL REPORTS , Security = A , Doc Type = BACKLOG

User Ref = 781108 , Acc Date = 25-Jun-86

REPORT NUMBER CTL/C/00613 CATEGORY B
ISSUE DATE 08 NOV 78
TITLE

2-AMINO-4,5-DIHYDRO-6-METHYL-5-OXO-4-PROPYL-S-TRIAZOLO(1,5-A
THE TOXICITY OF ORALLY ADMINISTERED EMETIC PP796 IN CYNOMOLGUS
MONKEYS
EMETIC RESPONSE
ORAL DOSING

SPONSOR PPD
CONTRACT LAB. HRC
CONTRACT NO. HRC ICI 171/78627
Y NUMBER Y00706/000
H NUMBER H14061
MISC DETAILS MONKEY

DIV REF

Subfile = CTL REPORTS , Security = A , Doc Type = BACKLOG

User Ref = 790319 , Acc Date = 25-Jun-86

REPORT NUMBER CTL/C/00700 CATEGORY B
ISSUE DATE 19 MAR 79
TITLE

GRAMOXONE W
PARAQUAT
2-AMINO-4,5-DIHYDRO-6-METHYL-5-OXO-4-PROPYL-S-TRIAZOLO(1,5-A
THE ACUTE ORAL TOXICITY AND MODE OF ACTION OF EMETIC PP796 IN
CYNOMOLGUS MONKEYS, AND ITS EFFECT UPON THE ACUTE ORAL

TOXICITY OF SEVERAL FORMULATIONS OF PARAQUAT
EMETIC RESPONSE
ORAL DOSING
RETENTIONSPONSOR PPD
CONTRACT LAB. HRC
CONTRACT NO. HRC ICI 119/78556
Y NUMBER

DIV REF

Y00706/000

Y00061/000

H NUMBER H14061

MISC DETAILS MONKEY

Subfile = CTL REPORTS , Security = A , Doc Type = BACKLOG

User Ref = 790621 , Acc Date = 25-Jun-86

REPORT NUMBER CTL/C/00728 CATEGORY B

ISSUE DATE 21 JUN 79

TITLE ETHYLENE GLYCOL

2-AMINO-4,5-DIHYDRO-6-METHYL-5-OXO-4-PROPYL-S-TRIAZOLO(1,5-A
THE EFFECTS OF EMETIC PP796 ON THE ORAL TOXICITY OF ETHYLENE
GLYCOL IN CYNOMOLGUS MONKEYS

EMETIC RESPONSE

ORAL DOSING

SPONSOR PCD
CONTRACT LAB. HRC
CONTRACT NO. HRC ICI 292/79470
Y NUMBER

DIV REF

Y00836/000

Y00706/001

H NUMBER H00402 H14061

MISC DETAILS MOUSE

Subfile = CTL REPORTS , Security = A , Doc Type = BACKLOG

User Ref = 770916 , Acc Date = 25-Jun-86

REPORT NUMBER CTL/C/00746 CATEGORY B

ISSUE DATE 16 SEP 77

TITLE E605

2-AMINO-4,5-DIHYDRO-6-METHYL-5-OXO-4-PROPYL-S-TRIAZOLO(1,5-A
THE EFFECTS OF EMETIC PP796 ON THE ORAL TOXICITY OF PARATHION IN
CYNOMOLGUS MONKEYS

EMETIC RESPONSE

ORAL LD50

ORAL DOSING

SPONSOR PPD
CONTRACT LAB. HRC
Y NUMBER

DIV REF

Y00706/000

H14061

MISC DETAILS MONKEY

Subfile = CTL REPORTS , Security = A , Doc Type = BACKLOG

User Ref = 791010 , Acc Date = 25-Jun-86

REPORT NUMBER CTL/C/00775 CATEGORY B

ISSUE DATE 10 OCT 79

TITLE FURADAN

2-AMINO-4,5-DIHYDRO-6-METHYL-5-OXO-4-PROPYL-S-TRIAZOLO(1,5-A
THE EFFECTS OF EMETIC PP796 ON THE ORAL TOXICITY OF FURADAN IN
CYNOMOLGUS MONKEYS

EMETIC RESPONSE

ORAL DOSING

SPONSOR PPD
CONTRACT LAB. HRC
CONTRACT NO. HRC ICI 282/79469
Y NUMBER

DIV REF

Y00611/000

Y00706/001

M224731

26 JAN 1990 11.14

Page 00003

H NUMBER H00762 H14061

MISC DETAILS MONKEY

Subfile = CTL REPORTS , Security = A , Doc Type = BACKLOG

User Ref = 770301 , Acc Date = 28-Jun-86

REPORT NUMBER CTL/P/00338 CATEGORY B

ISSUE DATE 01 MAR 77

TITLE 2-AMINO-4,5-DIHYDRO-6-METHYL-5-OXO-4-PROPYL-S-TRIAZOLO(1,5-A
PP796: SHORT-TERM PREDICTIVE TESTS FOR CARCINOGENICITY - RESULTS
FROM THE AMES TEST

AUTHORS E LONGSTAFF

SPONSOR PPD

DIV REF

Y NUMBER

H NUMBER H14061

MISC DETAILS SALMONELLA

Subfile = CTL REPORTS , Security = A , Doc Type = BACKLOG

User Ref = 761001 , Acc Date = 01-Jul-86

REPORT NUMBER CTL/R/00390 CATEGORY B

ISSUE DATE 01 OCT 76

TITLE PP796
THE CONCENTRATION OF PP796 REQUIRED TO PRODUCE EMESIS IN
EXPERIMENTAL ANIMALS AND AN ESTIMATION OF THE EMETIC DOSE IN

MAN

AUTHORS MS ROSE

SPONSOR PPD

DIV REF

Y NUMBER Y00706/000

H NUMBER H14061

MISC DETAILS DOG

HUMAN

MONKEY

PIG

AMENDED 770201

Subfile = CTL REPORTS , Security = A , Doc Type = BACKLOG

User Ref = 761101 , Acc Date = 01-Jul-86

REPORT NUMBER CTL/R/00391 CATEGORY B

ISSUE DATE 01 NOV 76

TITLE PARAQUAT

PP796

THE EFFECT OF ADMINISTRATION OF AN EMETIC (PP796) ON PARAQUAT
TOXICITY IN DOG AND MONKEY

AUTHORS GR PARKINSON

MS ROSE

WJD LAIRD

SPONSOR PHARMS

DIV REF

Y NUMBER Y00706/000

Y00061/000

H NUMBER H14061

MISC DETAILS DOG

MONKEY

Subfile = CTL REPORTS , Security = A , Doc Type = BACKLOG

User Ref = 791019 , Acc Date = 01-Jul-86

REPORT NUMBER CTL/R/00489 CATEGORY B

ISSUE DATE 19 OCT 79

TITLE PARAQUAT

2-AMINO-4,5-DIHYDRO-6-METHYL-5-OXO-4-PROPYL-S-TRIAZOLO(1,5-A

THE EFFECT OF PP796 ON GASTRIC EMPTYING IN RATS, MICE AND

MONKEYS AND ON PARAQUAT ABSORPTION IN RATS

AUTHORS AF WRIGHT

I WYATT

MS ROSE

SPONSOR PPD

DIV REF

NUMBER Y00061/000
H NUMBER H14061
MISC DETAILS MONKEY
MOUSE
RAT

Subfile = CTL REPORTS , Security = A , Doc Type = BACKLOG

User Ref = 790320 , Acc Date = 02-Jul-86

REPORT NUMBER CTL/T/01277 CATEGORY B

ISSUE DATE 20 MAR 79

TITLE ICI 63197

SKIN AND EYE IRRITATION, SKIN SENSITISATION POTENTIAL AND
RESPIRABLE FRACTION ANALYSIS

AUTHORS SE MOSES

SPONSOR PHARMS

DIV REF

Y NUMBER

H NUMBER H14061

MISC DETAILS GUINEA PIG

RABBIT

RAT

Subfile = CTL REPORTS , Security = A , Doc Type = BACKLOG

User Ref = 851219 , Acc Date = 03-Jul-86

REPORT NUMBER CTL/T/02451 CATEGORY B

ISSUE DATE 19 DEC 85

TITLE PP796

TKPP

ACUTE TOXICITY STUDIES IN DOGS

AUTHORS A BRAMMER

M ROBINSON

SPONSOR PPD

DIV REF SA 67/85

STUDY NUMBER XD0580

Y NUMBER Y00706/016

Y04976/001

H NUMBER H36968 H14061

MISC DETAILS DOG

Subfile = CTL REPORTS , Security = A , Doc Type = REPORTS

Acc Date = 12-Sep-86

REPORT NUMBER CTL/T/02459 CATEGORY B

ISSUE DATE 06 MAR 86

TITLE PP796 EMETIC DOSE RESPONSE STUDY IN DOGS

SUMMARY

AUTHORS ALISON BRAMMER M ROBINSON

SPONSOR PPD

DIV REF SA67/85

CONTRACT LAB .

CONTRACT NO. .

DATE DD MMM YY

STUDY NUMBER XD1002

Y NUMBER Y00706/016

H NUMBER H14061

MISC DETAILS .

Subfile = CTL REPORTS , Security = A , Doc Type = REPORTS

Acc Date = 10-Nov-86

REPORT NUMBER CTL/L/01359 CATEGORY B

ISSUE DATE 08 SEP 86

TITLE PP796:

EMETIC EFFICACY IN A BLANK PARAQUAT FORMULATION

AUTHORS M A COLLINS

M ROBINSON

SPONSOR PPD

DIV REF .

CONTRACT LAB .

CONTRACT NO. .

DATE DD MMM YY

STUDY NUMBER XD1127

NUMBER
H NUMBER
MISC DETAILS

100706/016 100706/001
H14061 H00534
DOG

Subfile = CTL REPORTS , Security = A , Doc Type = REPORTS
Acc Date = 11-May-87
REPORT NUMBER CTL/T/02452 CATEGORY B
ISSUE DATE 23 JAN 86
TITLE PP796

EFFECTS OF STOMACH STATUS ON EMETIC EFFICACY IN DOGS
SUMMARY REPORT

AUTHORS ALISON BRAMMER M R ROBINSON

SPONSOR PPD

DIV REF SA67/85

CONTRACT LAB .

CONTRACT NO. .

DATE DD MMM YY

STUDY NUMBER XD0580

Y NUMBER Y00706/016

H NUMBER H14061

MISC DETAILS .

Subfile = CTL REPORTS , Security = A , Doc Type = REPORTS

Acc Date = 18-Jan-88

REPORT NUMBER CTL/L/01839 CATEGORY B

ISSUE DATE 17 DEC 87

TITLE PP796

GENETIC TOXICOLOGY SCREENING

AMES TEST

AUTHORS E J ASHBY

B M ELLIOTT

R D CALLANDER

L L SMITH

SPONSOR PPD

DIV REF SC12/87

CONTRACT LAB .

CONTRACT NO. .

DATE DD MMM YY

STUDY NUMBER YV2161

Y NUMBER Y00706/020

H NUMBER H14061

MISC DETAILS SALMONELLA TYPHIMURIUM

Subfile = CTL REPORTS , Security = A , Doc Type = REPORTS

Acc Date = 15-Feb-88

REPORT NUMBER / / CATEGORY B

ISSUE DATE 06 OCT 76

TITLE 5H-S-TRIAZOLO(1,5-A)PYRIMIDIN-5-ONE
FINAL SHORT TERM CARCINOGENESIS REPORT SHEET
SR76204

AUTHORS E LONGSTAFF

J ASHBY

DIV REF .

SPONSOR .

CONTRACT LAB .

CONTRACT NO. .

DATE DD MMM YY

STUDY NUMBER .

Y NUMBER .

H NUMBER H14061

MISC DETAILS AMES TEST NEGATIVE

INCLUSION LEVEL
DATA/CORRESPONDENCE

Author: Bob Scott [CTL]

Date: 12-Jan-1993 10:40

TO: Remote Addressee

(tp@a1@uwgvax)

CC: N.N. Sabapathy

(SABAPATHY NN@a1@FHVAXC)

CC: Stan Chart

(CHART IS@a1@FHVAXC)

Subject : PP796 Inclusion Levels

Tim,

I am able to provide some comments on the letter from Steve Heyings.

Based on an assessment of the available animal and human data on the emetic effects of PP796 it was decided that a dose of 5mg was needed to ensure early and effective emesis. Thus, for a 70kg individual this represents a dose of 0.07mg/kg. This dose is precisely in the effective range as cited in Steve Heyings letter (0.03-0.11).

This dose must be present in the minimum potentially toxic dose of a PQ formulation. Although no absolute data are available for MAN, the MLD is considered to be around 40mg/kg, or, around 3000mg in a 70kg man.. This amount would be present in about 15ml of a 200g/l PQ ion formulation). Thus, the minimally potentially toxic dose is less than 40mg/kg and so the effective dose of PP796 must be present in a volume of formulation which is less than the MLD volume.

It was decided that the effective dose must be present in a 10ml volume of a 200g/l formulation.

Thus, 5mg must be contained in 10ml i.e 0.5mg/ml, or 0.05%.

All the information you sent me indicated that PP796 is present at this level in your products. It seems that you have it right, based on the original decisions for inclusion levels.

I can understand how Steve arrived at his suggestion that the PP796 levels are, perhaps, too high by a factor of 10. He has assumed that an (reliable) effective dose can be as low as 0.03mg/kg and that this can be present in a volume of formulation which is regarded as 2X MLD volume. This is not the position we can support.

I hope this clarifies the situation and you can assure Steve that the PP796 inclusion levels are indeed NOT 10X too high in your products.

Bob.

From
Dr J R Heylings
Biochemical Toxicology

ICI Central Toxicology Laboratory
Alderley Park
Macclesfield Cheshire SK10 4TJ

To
Dr S E Jagers
Executive Group

Tel: 0625 582711
Telex: 669095/669388
Fax: 0625 582897

Copies to

CC. RCS for info.

Your ref Our ref
 JRH101/LCM

Direct line
Redacted - EU PI

Tel ext
Redacted - EU PI

Date
9 April 91

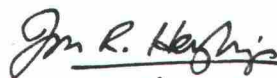
HUMAN DATA WITH THE PARAQUAT EMETIC PP796

I welcomed the opportunity we had to discuss the evidence surrounding the original decision to include PP796 at a concentration of 0.5mg/ml in Gramoxone.

As promised, I enclose some of the relevant background data which includes (i) correspondance on the emetic issue (ii) the original strategy document from Agrochemicals (EDC 729), which contains a copy of CTL/R/390 edited by MS Rose; and (iii) the relevant clinical trial data (PH 20992C) edited by PFC Bayliss.

As we discussed, the data presented in (ii) and (iii) differ markedly. The consequences of this, in my opinion, grossly misled the Agrochemicals Business when the decision to include a level of emetic "which would cause vomiting in the majority of people within 30 minutes following a single lethal dose" was made in 1976. I welcome your proposal for an independent assessment of the situation in order to confirm my findings.

The rationale for revisiting this 15 year old data is based in the impending decision to sanction a new emetic plant (estimated at £8m). I feel that the combination of current animal data with the emetic, together with the information I have brought to your attention, would convince the Business to sanction the cost of the emetic plant prior to the estimated date of 1993, the date which has been set as part of the Magnoxone development programme.


DR J R HEYLINGS
Biochemical Toxicology

$$\text{Inclusion level} = 0.5 \text{ mg/ml} \equiv 0.05\% \text{ w/v}$$

$$[200 \text{ g/L} = 20\%$$

$$2 \text{ g/L} = 0.2\%$$

$$1 \text{ g/L} = 0.1\%$$

$$1 \text{ mg/ml} = 0.1\%$$

$$0.5 \text{ mg/ml} = 0.05\% \quad \checkmark$$

CORRESPONDANCE : JAN 1990 - NOV 1990

From
Dr J R Heylings
Biochemical Toxicology

ICI Central Toxicology Laboratory
Alderley Park
Macclesfield Cheshire SK10 4TJ

To
L L Smith

Tel: 0625 582711
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CONFIDENTIAL

Copies to
S E Jagers
R S Morrod

Your ref Our ref
 JRH007/LCM

Direct line
Redacted - EU PII

Tel ext
Redacted - EU PII

Date
19 January 90

EMETIC CONCENTRATION IN PARAQUAT FORMULATIONS

I have reviewed the reports on studies involving the emetic PP796 (ICI 63197) between 1970 and 1986 produced by both ICI Pharmaceuticals and CTL. These studies involved oral dosing of this phosphodiesterase inhibitor in a number of species including man. This data has been previously reviewed in a CTL report (CTL/R/390) in 1976 and it was suggested that a concentration of 0.05% PP796 should be included in paraquat formulations to act as an emetic when lethal doses of paraquat were consumed.

Studies of poisoning cases involving emeticised paraquat formulations have not provided any definitive evidence that the introduction of 0.05% PP796 to paraquat concentrate in 1979 has resulted in a significant reduction in the number of fatalities attributed to the herbicide. This in my view, is not entirely surprising. My conclusion from studying the scientific evidence from clinical studies with the emetic is that the concentration of PP796 recommended in 1976 is probably well below an effective emetic dose in man.

All the animal studies which include dog, pig and primates are in agreement that the minimal effective doses of PP796 to induce >50% incidence of vomiting is 0.5mg/kg. Animal studies with PP796 suggest that both the incidence of vomiting and the time to vomit is dose dependent. Clinical studies with the emetic suggested that man was more sensitive than other species to the centrally acting emetic. However data presented to support this is insufficient to be scientifically valid. The potency effect of PP796 is based on one volunteer (out of one) who vomited at an emetic dose of 0.11mg/kg. On a physiological basis there is no reason why man should be more sensitive to emesis. Indeed, data with monkey, dog and pig (all acceptable models of GI function with pharmaceutical submissions to the FDA and CSM) suggest little or no species differences with PP796 to cause emesis.

The original recommendation for the concentration of emetic to be 0.05% was based on "a concentration which would cause vomiting should the minimal potential lethal dose of paraquat formulation be swallowed" (Hart and Whitehead 1984). If 20mg/kg paraquat represents such a minimal lethal dose to man, this would only contain 0.05mg/kg emetic. Thus, ten times this dose would have to be ingested to reach a minimally effective emetic dose of 0.5mg/kg, if there is no species variation.

Cont...

My personal viewpoint, based on scientific judgement of available toxicological data together with the extensive clinical poisoning data, is that the concentration of PP796 should be increased by ten fold from 0.05% to 0.5% in GRAMOXONE. This reduces the PQ: Emetic ratio from 400 to 40. By calculation, I recommend the following levels of emetic to be added to our commercial formulations. This is based on the bipyridyl content: emetic being 40:1.

| FORMULATION | Bipyridyl % | Current Emetic % | Recommended Emetic % |
|------------------|----------------|---------------------|-------------------------|
| GRAMOXONE EXPORT | 20 | 0.05 | 0.5 |
| GRAMOXONE L | 10 | 0.05 | 0.25 |
| PREEGLOX | 9 | 0.05 | 0.23 |
| WEEDOL | 5 | 0.04 | 0.13 |

I have summarized the important issues in the attached document, and I would welcome a debate on this suggestion.

Jon R. Heylings
J R HEYLINGS
Biochemical Toxicology

REVIEW OF THE EMETIC CONCENTRATION IN PARAQUAT FORMULATIONS

CTL EMETIC STUDY CTL/T/2459 1985 (DOG)

0.5mg/kg PP796 is the minimum effective dose in dogs
(0.1mg/kg PP796 had no effect in dogs).

CTL EMETIC/PARAQUAT STUDY CTL/T/2471 1985 (DOG)

0.5mg/kg PP796 is the minimum effective dose to reduce
paraquat toxicity, peak plasma and AUC values (10X).

Dosing solution 0.296% PQ + 0.0074% PP796

PQ: Emetic ratio = 40

PQ Dose = 20mg/kg (lethal)) SURVIVAL

PP796 = 0.5mg/kg (effective))

GRAMOXONE EXPORT (20% PQ + 0.05% PP796)

PQ: Emetic ratio = 400

PQ Dose = 20mg/kg (lethal)) DEATH (IRI STUDY 1987)

PP796 = 0.05mg/kg (ineffective))

Dogs would require a minimum of $10 \times 20 = 200\text{mg/kg}$

PQ to introduce an effective emetic dose. This represents
SEVENTEEN TIMES the LD50 in Dogs.

PREEGLOX (Ex DQ 4.5% PQ + 0.05% PP796)

PQ: Emetic ratio = 90 (Bipyridyl: Emetic ratio = 180)

PQ Dose = 20mg/kg (lethal)

Bipyridyl dose = 20mg/kg (lethal)

PP796 Dose = 0.22mg/kg (ineffective) PP796 Dose = 0.11mg/kg

DEATH (IRI STUDY)

(ineffective)

DEATH (IRI STUDY)

CTL EMETIC STUDY CTL/R/391 1976 (DOG/MONKEY)

2mg/kg PP796 used in both species successfully
(proved later to be 4x effective emetic dose).

Dosing solution (Dog) 0.4% PQ + 0.04% PP796

PQ = Emetic ratio = 10

PQ Dose = 20mg/kg (lethal)) SURVIVAL (both species)

PP796 = 2mg/kg (effective))

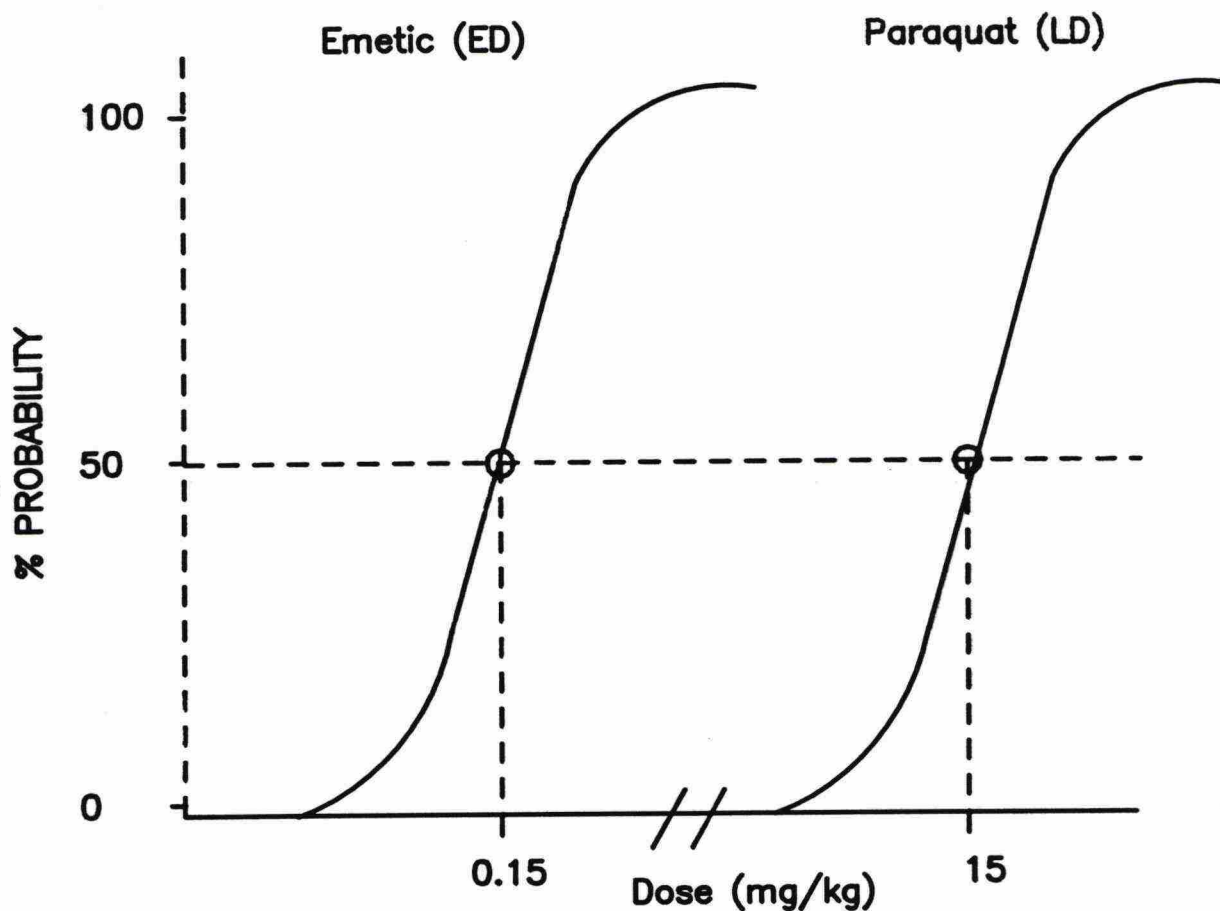
CTL EMETIC DOSE ESTIMATION IN MAN CTL/R/390 1976

PP796

| mg | mg/kg | n | No vomiting | % |
|------|--------|--------|-------------|-------------------------|
| 0.25 | 0.0035 | 1 | - | - |
| 0.5 | 0.007 | 1 | - | - |
| 1 | 0.015 | 2 | 0/2 | 0 |
| 2 | 0.03 | 3 + 34 | 4/37 | 11 |
| 3* | 0.04 | 2 | - | - * Carried out but not |
| 4 | 0.06 | 2 | 1/2 | 50 stated in report. |
| 8 | 0.11 | 1 | 1/1 | 100 (<- What if 0/1?) |

Addendum

PARAQUAT TO EMETIC RATIO



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

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

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

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

or

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

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 $\frac{3}{4}$ - 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. V 0.5 |
| 11 | 4.0 | Dizziness, flushing of face, sweating from $\frac{1}{2}$ - 2 hours. |
| 12 | 8.0 | At 30 minutes sweaty, flushed and light headed. Vomited at 2 hours. V 2 |

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 $1\frac{1}{2}$ and $3\frac{1}{2}$ 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.

EVIDENCE FOR MAN BEING MORE SENSITIVE TO PP796

SCIENTIFIC ARGUMENT

- (i) Dose Response Data - Insufficient evidence based on one volunteer at 0.1mg/kg.
 - Not statistically proven
 - No evidence of D/R in man
 - Even if present data was proven it makes man only 5x more sensitive not 10x.
 - Doses below 0.5mg/kg are not dose related in animals.
- (ii) Delay in Absorption - Possibly by a few minutes but unlikely to affect outcome .
 - Lipophilic compound.
 - Adding solid PP796 to a capsule caused vomiting within 15 min in dogs.
- (iv) Synergism between emetic and PQ inducing vomiting
 - Constant factor between species if important.
 - PQ vomiting effect occurs after peak plasma values therefore of no use.
 - CTL studies proved that 0.5mg/kg required with 20mg/kg PQ.
- (v) Species variability - No physiological basis with centrally acting emetics.
 - Pig, Dog, Monkey all respond only at 0.5mg/kg
 - No reason why unsuspecting humans should respond at a lower dose.

GENERAL POINTS IN CTL/R/390 REPORT CONCLUSION

Principal Reasons for 5mg PP796 in 10ml (0.05%) being recommended in 1976.

- (i) "Irritant nature of formulation - No rationale for this at all.
would enhance vomiting response" PQ induced vomiting takes several hours. Time to vomiting is central to the argument.
- (ii) "Soluble dispersed form is more - Not proven and extremely unlikely
bioavailable than solid" with this compound. Solid PP796 causes vomiting in minutes in dogs.

The 1976 argument was based on people consuming several lethal doses. Even if this data was proven valid, suicides involving 1-2 lethal doses would not vomit - nor would the ACCIDENTAL poisonings.

PROBLEMS ASSOCIATED WITH INCREASING EMETIC CONCENTRATION
FROM 0.05% to 0.5% IN AQUEOUS PARAQUAT CONCENTRATES

- SIDE EFFECTS?** Emesis is the chief side effect in man.
PP796 would not have achieved development status if there had been serious toxicity problems.
Dogs can tolerate 20mg/kg PP796. There were no treatment related bodyweight changes. Food consumption was 100% in all dogs at all times. Vomiting occurred within 10 min but had ceased by one hour. Dogs had fully recovered by 2-3 hours. This 20mg/kg dose of PP796 represents 400 times the effective emetic dose.
- COST?** Manufacturing costs may double but the Emulsion programme can bear a penalty of £1000 per tonne.
There would be no formulation, spray, herbicidal or development problems.
- REGISTRATION?** Level of PP796 in WEEDOL was doubled in 1985 from 0.02 to 0.04%. There are no registration difficulties below 5% additive concentrations.
- SOLUBILITY?** PP796 is poorly soluble in water. However, an aqueous solution of 1% can be made (CTL/T/2459). Therefore, GRAMOXONE with 0.5% should be feasible.

RESULT OF INCREASING EMETIC CONCENTRATION FROM 0.05% TO 0.5%
IN AQUEOUS PQ CONCENTRATES

1. Reduce the number of fatalities attributed to paraquat poisoning (especially accidentals and homicides).
2. Protect registration in established territories.
3. Open up new markets on the basis of improved safety.
4. Move back ultimately to higher strength concentrates.

From
Dr S E Jagers
Regulatory Toxicology Manager

ICI Central Toxicology Laboratory

Alderley Park
Macclesfield Cheshire SK10 4TJ

To
Dr J R Heylings
Biochemical Toxicology

Tel: 0625 582711
Telex: 669095/669388
Fax: 0625 582897
EDT: UKBLA99::SEJ1

Copies to
Dr R S Morrod
Dr L L Smith

Your ref Our ref
 SEJ/LMM

Direct line
Redacted - EU PII

Tel ext
Redacted - EU PII

Date
25 Jan 90

EMETIC CONCENTRATIONS

John,

Thank you for your letter of the 19th January I was surprised by the limited data on the emetic effects of this compound in man even bearing in mind the low popularity of emesis as a side effect. Are you certain that Pharmaceuticals Business has no further data.?



S E Jagers

Bayliss Pharmaceuticals Report

as quoted in Reference list in CTL/R/390 2.

Received April 9/ 81
PH18987C
Vol I

DRUG SUBSTANCE

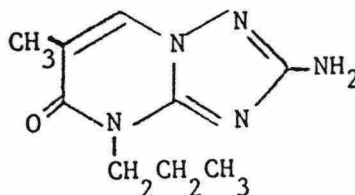
3. NAMES

- (i) Approved Name : Not yet selected
- (ii) Laboratory Code Number : I.C.I. 63,197
- (iii) Chemical Name : 2-Amino-6-methyl-5-oxo-4-n-propyl-4,5-dihydro-s-triazolo (1,5-a) pyrimidine

4. DESCRIPTION

- (i) Physical form : A white to pale cream powder
- (ii) Solubility : Soluble in 500 parts of water, in 12 parts of chloroform and in 170 parts of alcohol (95%).

(iii) Structural formula



(iv) Molecular formula

: $C_9H_{13}N_5O$

(v) Molecular weight

: 207.2

5. INTENDED USE

Evaluation of efficacy in the treatment of mental disease and respiratory disease.

RESULTSDetails of subjects studied

| No. | Initials | Age (yrs) | Sex | Weight (kg) | Dose ICI 63,197 (mg) |
|-----|----------|--------------|-----|----------------|-------------------------|
| 1 | ML | 23 | F | 50.5 | 0.25 |
| 2 | IL | 22 | M | 77.5 | 0.5 |
| 3 | HMcD | 21 | M | 65.5 | 1 |
| 4 | PL | 22 | M | 74.0 | 1 |
| 5 | MM | 20 | F | 56.5 | 2 |
| 6 | IMcL | 24 | F | 56.0 | 2 |
| 7 | N | 22 | F | 55.0 | 2 |
| 8 | PR | 21 | M | 79.0 | 3 |
| 9 | C | 23 | M | 72.0 | 3 |
| 10 | APC | 21 | M | 82.5 | 4 |
| 11 | CB | 23 | M | 80.0 | 4 |
| 12 | CC | 21 | M | 80.0 | 8 |

Blood levels of ICI 63,197

These are shown below (µg/ml.):-

| No. | Dose of ICI 63,197 (mg) | Time (hrs.) | | | | | | | |
|-----|-------------------------------|-------------|-------|-------|-------|-------|-------|-------|-------|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| 1 | 0.25 | 0.016 | 0.006 | 0.004 | 0.005 | | | | ND |
| 2 | 0.5 | 0.008 | 0.017 | 0.005 | 0.005 | | | | ND |
| 3 | 1.0 | 0.005 | 0.019 | 0.004 | 0.006 | | 0.005 | | 0.004 |
| 4 | 1.0 | 0.017 | 0.016 | 0.009 | 0.006 | | 0.008 | | |
| 5 | 2.0 | 0.018 | 0.034 | 0.024 | 0.018 | | 0.007 | | |
| 6 | 2.0 | 0.034 | 0.065 | 0.044 | 0.039 | | 0.015 | | 0.006 |
| 7 | 2.0 | 0.062 | 0.068 | | 0.056 | 0.044 | 0.037 | 0.031 | 0.025 |
| 8 | 3.0 | 0.044 | 0.031 | | | 0.006 | | 0 | 0 |
| 9 | 3.0 | 0.050 | 0.056 | | 0.044 | 0.031 | | 0.018 | 0.025 |
| 10 | 4.0 | 0.081 | 0.041 | 0.034 | 0.060 | | 0.01 | | 0.014 |
| 11 | 4.0 | 0.045 | 0.056 | 0.044 | 0.033 | | 0.016 | | 0.009 |
| 12 | 8.0 | 0.047 | 0.085 | 0.068 | 0.041 | | 0.029 | | 0.042 |

ND = not detected, i.e. < 0.004 µg/ml.

The half life varies from $1\frac{1}{2}$ - $3\frac{1}{2}$ hours in this series.

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 $\frac{3}{4}$ - 2 hours. |
| 9 | 3.0 | At 30 minutes dizzy, pale, sweating. Nausea marked. |
| 10 | 4.0 | Nausea and flushing at 15 minutes. <u>Vomited at 30 minutes.</u> Light headedness for 2 - 3 hours. |
| 11 | 4.0 | Dizziness, flushing of face, sweating from $\frac{1}{2}$ - 2 hours. |
| 12 | 8.0 | At 30 minutes sweaty, flushed and light headed. <u>Vomited at 2 hours.</u> |

V 0.5

V 2

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 $1\frac{1}{2}$ and $3\frac{1}{2}$ 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.

Date?
Reduced for?

THE EFFECT OF THE ADMINISTRATION OF PP796 ON PARAQUAT TOXICITY
IN THE DOG AND AN ESTIMATION OF THE EMETIC DOSE IN MAN

The decision to add the emetic PP796 to paraquat formulations was based on the effectiveness of PP796 in reducing the toxicity of paraquat in two species of experimental animal, namely the dog and monkey (CTL/R/391). It was shown that the approximate LD₅₀ of paraquat to the dog and monkey was increased by a factor between three and five and that this reduction in toxicity could be explained by a lowering of the paraquat in the plasma of animals administered with both paraquat and emetic compared with that of animals given paraquat alone (CTL/R/391). When it came to establishing the concentration of PP796 that should be added to Gramoxone, it was decided that the minimum lethal dose of formulation should contain a dose of PP796 likely to cause emesis. This dose was set at 5mg per person based on the results of limited clinical trials when PP796 was under development by Pharmaceuticals Division of ICI PLC as an anti-asthmatic drug. The inclusion rate in Gramoxone became 5mg per 10ml of Gramoxone (CTL/R/390).

When this decision was made it was thought that the clinician had many hours to remove paraquat from the stomach and lower intestine before lethal amounts of paraquat would be absorbed from the gastrointestinal tract into the plasma and then accumulated into the lung. It is now clear from the data collected from CTL (and elsewhere) that paraquat is absorbed rapidly from the gastrointestinal tract into the bloodstream such that after ingestion a peak concentration in the plasma is reached within one to 3hr. Therefore, in order to optimise the effectiveness of PP796 in reducing the toxicity of swallowed paraquat, not only must PP796 cause effective emesis but it must do so within a very short period of time.

ICI has continued to assess the effectiveness of PP796 addition to Gramoxone, particularly with regard to human poisonings. Although data from human poisoning cases has not shown a statistically significant reduction in mortality as a result of the addition of emetic, the addition has reliably caused spontaneous vomiting in man (Bramley and Hart, 1981). However, it has not been possible from human data, to determine whether sufficient emetic has been added to cause the earliest possible onset of spontaneous vomiting.

In order to answer this question, a series of laboratory studies has been conducted using dogs as animal models. Copies of reports of these studies are attached. In summary, these studies showed that:-

dog v. man

- 1) The amount of emetic given to dogs alters the time to vomiting. 0.1mg PP796/kg does not cause vomiting whereas 0.5mg/kg causes vomiting within 30min and 3mg/kg or greater cause vomiting within 10min (CTL/T/2459, CTL/T/2451 and CTL/T/2471).

*But of
JH 1990/91
data + PQ.*

- 2) Doses of 20mg PP796/kg appear to be supermaximal and may cause harm to the dogs (CTL/T/2459 and CTL/T/2471).
- 3) When a toxicologically significant dose of paraquat (20mg/kg) is given to dogs along with various doses of PP796 it was found that 0.5mg PP796/kg reduced the absorption of paraquat by approximately 10-fold and 3mg/kg or 20mg/kg by approximately 50-fold (CTL/T/2471).

These data lead to the simple conclusion that, after swallowing paraquat, rapid and effective vomiting reduces the absorption of the bipyridyl and its toxicity will be reduced..... *in the dog.*

In the context of human poisoning cases in Japan, the following approximations have been made:

If we assume that,

- 1) the average body weight of a Japanese adult to be 50kg
- 2) the minimum lethal dose is 10ml Gramoxone (contains 5mg PP796)

then the dose level of emetic in a minimum lethal dose of paraquat is 0.1mg PP796/kg.

This is well short of the optimum concentration range of emetic found in the dog studies which lies between 0.5mg PP796/kg and 3mg/kg.

Since the formulation of paraquat will be diluted from 20% paraquat cation to 4.5% paraquat cation and 4.5% diquat cation (Preeglox L) and assuming that the contribution of diquat to the toxicity of the formulation is minimal, then the minimal lethal dose of Preeglox L will be in the range of 40-50ml. By increasing the dose of emetic to 40mg in 40ml (0.1%) then the dose of emetic in one mouthful (approximately 40ml) will approach 1mg/kg (i.e. in the range of

that which is optimal in the dog). There will also be the important additional advantage in that dilution will increase the volume of formulation which contains a lethal dose of paraquat. Also, by increasing the volume of stomach contents prior to emesis may well result in more effective emesis with an increased proportion of stomach contents being removed.

The combination of the data from the dog studies together with our understanding of the absorption of paraquat in man leads to the conclusion that very rapid emesis (within 10-15min) may be effective in reducing the toxicity of Preeglox L. On the basis of the calculations given before it would appear sensible to add at least 0.1% PP796 to the Preeglox L formulation in order to optimise the likelihood of very rapid emesis in cases of human poisoning.

It has been suggested that an increase in the concentration of emetic in Preeglox L from that which is in Gramoxone may lead to the danger of excessive vomiting or difficulty in treating vomiting patients with Fullers Earth or other appropriate absorbants. However, the potential advantages in reducing the overall mortality rate by the introduction of 0.1% PP796 Preeglox L formulation appear to greatly outway these possible problems. Furthermore, from the dog studies, a 50kg patient would have to drink 500ml Preeglox L containing 0.1% PP796 before they would have taken 10mg PP796/kg. This is half the dose level indicated in the dog studies at which PP796 itself would exert possible harmful effects. However, it is extremely rare for patients to drink such large volumes of paraquat containing formulation.

Only...
If dog =
man
+
dog DRC
is right.

In conclusion, an assessment of the available data on the effectiveness of PP796 in inducing vomiting, in animal models and man leads to the conclusion that increasing the concentration of PP796 to 0.1% in Preeglox L is justified.

Reference

Hart TB and Bramley A. Paraquat poisoning in UK. Human Toxicology 2 417 (1983).

L L SMITH

Senior Scientist and
Paraquat Product Manager

Date?

File
TBH
Facsimile fromImperial
Chemical
Industries
PLC

CENTRAL TOXICOLOGY

LABORATORY

Alderley Park Macclesfield
EnglandTO T B HART
PPD FERNHURSTFROM L L SMITHnumber of pages 4 excluding this pageDate 14.2.86

| C/LATE | SEND TO | P/COPY |
|--------|---------|--------|
| | | |
| B/F | | |

Please Reply DIRECT to C.T.L.

Facsimile Number 0625 582897

Telephone Number 0625 582711

extn

Redacted - EU PII

or

Redacted - EU PII

Direct Line

F A C S I M I L E M E S S A G E**From****L L Smith
Biochemical Toxicology****Imperial Chemical Industries PLC
Central Toxicology Laboratory****Alderley Park Nr Macclesfield
Cheshire SK10 4TJ****To****R D N Birtley
T B Hart
Plant Protection Division
Fernhurst****Telephone Alderley Edge 0625 582711
Direct Line Redacted - EU PI****Copies to****Your ref****Our ref****Tel ext****Date****LLS/SAB/Fax**Redacted - EU PI**14 Feb 86****THE EFFECT OF THE ADMINISTRATION OF PP796 ON PARAQUAT TOXICITY IN THE DOG AND AN
ESTIMATION OF THE EMETIC DOSE IN MAN****Please find enclosed DRAFT document. I would appreciate your comments by
20th February.****Thank you.***Sally***PP LEWIS L SMITH
Senior Scientist and
Paraquat Product Manager****Enc**

DRAFT

THE EFFECT OF THE ADMINISTRATION OF PP796 ON PARAQUAT TOXICITY IN THE DOG AND AN ESTIMATION OF THE EMETIC DOSE IN MAN

~~The emetic PP796 was added to formulations of paraquat in the late 1970's.~~
to add PP796 to paraquat formulations

This decision was based on the effectiveness of PP796 in reducing the toxicity of paraquat in two species of experimental animal, namely the dog and monkey (CTL/R/391). It was shown that the approximate LD₅₀ of paraquat to the dog and monkey was increased by a factor between three and five and that this reduction in toxicity could be explained by a lowering of the paraquat in the plasma of animals administered with both paraquat and emetic compared with that of animals given paraquat alone (CTL/R/391). When it came to establishing the concentration of PP796 that should be added to Gramoxone, it was decided that the minimum lethal dose of formulation should contain a dose of PP796 likely to cause emesis. This dose was set at 5mg per person based on the ^{results of} ~~response~~ *limited clinical trials* of a few humans who had been given PP796 when it was under development by Pharmaceuticals Division of ICI PLC as an anti-asthmatic drug. The inclusion rate in Gramoxone became 5mg/10ml of Gramoxone (CTL/R/390).

** See attached sheet*

When this decision was made it was thought that the clinician had many hours to remove paraquat from the stomach and lower intestine before lethal amounts of paraquat would be absorbed from the gastrointestinal tract into the plasma and then accumulated into the lung. It is now clear from the data collected from CTL (and elsewhere) that paraquat is absorbed rapidly from the gastrointestinal tract into the bloodstream such that the majority of the paraquat that is absorbed will be present in the blood within a few hours of ingestion and a peak concentration in the plasma is reached within one to 3hr. Therefore, to be effective in reducing the toxicity of swallowed paraquat, not only must PP796 cause effective emesis but it must do so within a very short period of time. There is good evidence that with the present inclusion rate PP796 is an effective emetic. However, it seems very doubtful that a significant percentage of paraquat poisoned patients vomit within 10min of ingestion. It can be seen from the attached draft reports of studies carried out in dogs that it is necessary to induce vomiting very shortly after swallowing paraquat in order to maximise the reduction in the absorption of paraquat. These studies showed that:

- 1) The amount of emetic given to dogs alters the time to vomiting. 0.1mg PP796/kg does not cause vomiting whereas 0.5mg/kg causes vomiting within 30min and 3mg/kg or greater cause vomiting within 10min (CTL/T/2459, CTL/T/2451 and CTL/T/2471).

DRAFT

- 2 -

2) Doses of 20mg PP796/kg appear to be supermaximal and may cause harm to the dogs (CTL/T/2459 and CTL/T/2471).

3) When a toxicologically significant dose of paraquat (20mg/kg) is given to dogs along with various doses of PP796 it was found that 0.5mg PP796/kg reduced the absorption of paraquat by approximately 10-fold and 3mg/kg or 20mg/kg by approximately 50-fold (CTL/T/2471).

These data lead to the ~~simple~~ conclusion that, after swallowing paraquat, rapid and effective vomiting reduces the absorption of the bipyridyl and its toxicity will be reduced.

~~The data in man does not indicate that PP796 causes rapid vomiting (within 10min). In some cases where vomiting has been reported very soon after swallowing and emesis has been sustained, the patients have swallowed large amounts of formulation. In these cases, large doses of PP796 have been taken which induces rapid and sustained emesis. However, large amounts of paraquat will also have been consumed (this can approach x10 or x15 the LD50 dose of paraquat), in which case it is very unlikely that even rapid emesis will prevent the absorption of a lethal dose of paraquat.~~

In the context of human poisoning cases in Japan, the following approximations have been made:

If we assume,

- 1) The average body weight of a Japanese to be 60kg
- 2) The minimum lethal dose is 10ml Gramoxone (contains 5mg PP796)

then the dose level of emetic in a minimum lethal dose of paraquat is 0.1mg PP796/kg.

This is well short of the optimum concentration range of emetic found in the dog studies which lies between 0.5mg PP796/kg and 3mg/kg.

Assuming the formulation of paraquat diluted from 20% paraquat cation to 4.5% paraquat cation and 4.5% diquat cation (Praeglox L) and that the contribution of

DRAFT

diquat to the toxicity of the formulation is minimal, then the minimal lethal dose of Preeglox L will be in the range of 40-50ml. ^{By increasing the dose of emetic to 40mg in 40ml (0.1%) then the dose of emetic in one mouthful} ~~0.1% from 0.05% (equivalent to 40 mg in 40 ml) from 0.05%~~

(approximately 40ml) will approach 1mg/kg (i.e. in the range of that which is optimal in the dog). There will also be the important additional advantage in that dilution will increase the volume of formulation which contains a lethal

dose of paraquat. ^{Increasing the volume of stomach contents prior to emesis} ~~This means that if emesis occurs and only 50% of the stomach contents are removed it is less likely that a lethal quantity of paraquat will remain in the stomach (c.f. if 40ml of Gramoxone is swallowed and 20ml vomited, a lethal dose would remain).~~

with

proportion.

The combination of the data from the dog studies together with our understanding of the absorption of paraquat in man leads to the conclusion that very rapid emesis (within 10-15min) ^{may} ~~ought~~ to be effective in reducing the toxicity of Preeglox L. On the basis of the calculations given before it would appear sensible to add at least 0.1% PP796 to the Preeglox L formulation in order to optimise the likelihood of very rapid emesis in cases of human poisoning.

It has been suggested that an increase in the concentration of emetic in Preeglox L from that which is in Gramoxone may lead to the danger of excessive vomiting or difficulty in treating vomiting patients with Fullers Earth or other appropriate absorbents. However, the potential advantages in reducing the overall mortality rate by the introduction of 0.1% PP796 Preeglox L formulation appear to greatly outway these possible problems. Furthermore, from the dog studies, a 50kg patient would have to drink 500ml Preeglox L containing 0.1% PP796 before they would have taken 10mg PP796/kg. This is half the dose level indicated in the dog studies. In addition, it is extremely rare for patients to drink such large volumes of paraquat containing formulation.

In conclusion, an assessment of the available data on the effectiveness of PP796 ^{in animals models and man} ~~in inducing vomiting together with the understanding of the pharmacokinetics of paraquat in cases of human poisoning~~ leads to the conclusion that increasing the concentration of PP796 to 0.1% in Preeglox L is fully justified.

Sally

PP L L SMITH
Senior Scientist and
Paraquat Product Manager

From:
Jane Botham
Information Services Section
Al.7
CTL

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To:
Dr. N. Sabapathy
Product Safety Section
ICI Agrochemicals
Fernhurst

Copies to:

| | |
|--------------|------|
| Dr. R. Scott | CTL |
| Mr. S. Chart | RAD |
| Dr. L. Brown | SHED |

Your ref

Our ref

Tel ext

Date

20-May-1991

Redacted - EU PG

EMETIC AND PARAQUAT POISONING

Dear Dr. Sabapathy,

I have checked our files for papers on the effect of the addition of emetic to paraquat formulations. As you suspected, there is little published data. One abstract (Denduyts-Whitehead, A et al J. Tox. Clin. Tox 23 422-3 1985) does mention the addition of the emetic to paraquat formulations but, unfortunately, does not quote any useful data. I can only assume that any data quoted at the presentation to which this abstract refers was obtained from:-

Hart, T.B. and Whitehead, A
Effect of the addition of an emetic to paraquat formulations on acute poisoning in man.

A copy of this paper is enclosed for your interest. However, an extensive search of both internal and external databases has failed to reveal any evidence that this paper was ever published. The paper enclosed is at the draft stage at which comments were requested, and has therefore not been peer-reviewed and should probably not be quoted.

Another abstract, presumably presented at the same meeting as the Denduyts-Whitehead paper, although not quoting any data does mention that the addition of emetic to paraquat formulations does not seem to have had any significant effect.

One other paper mentioning the emetic is that of Onyon and Volans (Human Toxicol 6 19-29 1987). This paper (copy enclosed) mentions the use of animal data to support the calculated dose of emetic to be added to formulations. The reports quoted are, of course, available in CTL if you do not have copies.

I hope that this information will be helpful,

Regards,

Jane

From
Dr S E Jagers
Regulatory Toxicology Manager

ICI Central Toxicology Laboratory
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Macclesfield Cheshire SK10 4TJ

To
Dr G J A Oliver

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Copies to
Dr J R Heylings
Dr R C Scott

| | | | | |
|----------|---------|-------------------|-------------------|-----------|
| Your ref | Our ref | Direct line | Tel ext | Date |
| | SEJ/LMM | Redacted - EU PII | Redacted - EU PII | 26 Apr 91 |

CTL RECOMMENDATIONS FOR EMETIC INCLUSION LEVELS IN GRAMOXONE

CTL Review Team

I believe it appropriate for CTL to review its data base and recommendations made to the Agrochemical Business for the inclusion level of emetic in paraquat formulations. It is quite routine for us to review our positions from time to time. The Business is currently considering a new emetic plant and clearly inclusion levels could impact on the consideration of the capacity of such a plant. At the same time Dr Smith has left the Laboratory and a new team is accountable for the Laboratory position and representing it within the Business.

Dr Smith has been recommending to the Business for some time that the emetic level in gramoxone should be increased. While it is unlikely that the direction of our recommendation will change Dr Heylings has also made representations to me that the force with which our argument can be put would be increased by a modern review of the data base.

Accordingly I am asking you to lead a small team of Dr Heylings as an emetic and formulation expert and Dr Bob Scott as paraquat Produce Manager to address the issue.

Contd/

The remit of the team is to;

1. Review all the pertinent existing data relevant to the selection of the inclusion level of the emetic PP796 in Gramoxone and other Paraquat formulations. The review to include data from the dog and man.
2. To confirm or derive a new recommendation for the Laboratory on the inclusion level of emetic. I require the recommendation to display the likely outcome of several different levels or 'bands' of emetic inclusion together with the advantages and disadvantages of each. I require assurance that there are not upper levels of emetic inclusion which might compromise the patient.

I would emphasize that I wish the review to be comprehensive, constructive and forward looking. This is not a request for a long document, I leave it to you to judge what is required to clarify and support recommendations. The report should be prepared for me. In the interest of economy it may be appropriate that the report is in a form which is eventually suitable for sharing with the Business and conveying our recommendations. However I leave it to you to judge again whether a report to me and to the Business are compatible or not. It may be that a separate report will be required to display the information to the Business in a form that is clear to non toxicologists.

I would like to receive the report by the end of June:



S E Jaggars

From

Dr L L Smith
Biochemical Toxicology

ICI Central Toxicology Laboratory

Alderley Park
Macclesfield Cheshire SK10 4TJ

To

J R Heylings
Biochemical Toxicology

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Dr S E Jagers

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Our ref

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Date

LLS438/JJB

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6 November 1990

RE: HUMAN DATA WITH PARAQUAT FORMULATIONS CONTAINING PP796.

Thank you for your memo of the 5 September 1990 discussing several issues associated with the concentration of emetic in formulations of paraquat. It is clear from the data you presented that there was probably some misunderstanding or confusion in the way the case for the inclusion rate of 796 at 0.05% was arrived at. However, I am sure you will appreciate that in attempting to reconsider the thinking and knowledge in 1976 when this decision was taken is extremely difficult. If my memory serves me correctly it was not even partly appreciated that the time to emesis in man that is required to prevent the absorption of paraquat is less than 30 minutes. In the mid 1970's we were still influenced by the data in rat which has an entirely different plasma paraquat profile to that of man.

Another important concern was the generation of prolonged, severe vomiting which would occur in patients who had consumed very large quantities of Gramoxone containing the emetic. This concern has been experienced in Japan. Several Japanese Doctors have expressed serious reservations at the difficulty of treating patients who have consumed large quantities of Gramoxone, due to prolonged and severe vomiting. I do not agree with their viewpoint and we have resisted this with the Regulatory Authorities. However, in a final analysis it is Regulatory Authorities that decide the level of inclusion that is acceptable.

As you are aware, I, and others at CTL, came to the view some years ago that it would be useful to increase the concentration of emetic in paraquat formulations. This view was arrived at on the basis on our experience of human poisoning and some experimental data generated in dogs. The dog data was much less comprehensive than the data you have subsequently obtained.

continued.....

However, it appears that there is no disagreement between us that an increase in emetic of 3-5 fold ought to be evaluated. I would emphasise that I cannot advise the Business that such an increase would certainly reduce the number of human fatalities. It is my experience that extrapolating data in experimental animals to man is not particularly easy with paraquat. However, I believe there is an opportunity to combine the increase in emetic concentration with the inclusion of Trisilicate to reduce the toxicity of paraquat formulations. Both Stuart and myself are fully supportive of seeing such a formulation evaluated in a few well controlled and well understood markets so as to establish whether there is an opportunity to reducing paraquat fatalities resulting from the intentional ingestion of the paraquat formulations.

In conclusion I do not intend to pursue any further the reasons for the inclusion of PP796 at 0.05% as decided in the early part of 1976. Rather, I wish to concentrate our efforts in agreeing a strategy with the Business that will prompt us to evaluate formulations of paraquat that are intrinsically less toxic and contain increased concentrations of emetic.

Lewis
DR L L SMITH

From

Dr L L Smith
Biochemical Toxicology

To

Dr J R Heylings
Biochemical Toxicology

ICI Central Toxicology Laboratory

Alderley Park
Macclesfield Cheshire SK10 4TJ

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Our ref
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Direct line

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Tel ext

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Date

11 October 1990

For the record this is to confirm I received your memo of the 5 September 1990 discussing the generation of human data on the emetic PP796. In my capacity as Paraquat Project Manager, I will ensure that this matter is raised with the Business.



Lewis Smith

From

Dr L L Smith
Biochemical Toxicology

To

Dr S E Jagers
Executive Group

ICI Central Toxicology Laboratory

Alderley Park
Macclesfield Cheshire SK10 4TJ

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Date
11 October 1990

Please find enclosed briefing note from Jon Heylings to me on the human data which was presented in the mid-70's to support the inclusion of PP796 in formulations of paraquat. I have discussed this issue several times with Jon and have made it clear to him that with regard the bottom line I have been a supporter of increasing the concentration of emetic in paraquat for many years. The reasons for my decision include some of the points that Jon has raised, but also the suggestion of toxicity studies that were carried out in the mid-80's and 15 years of experience in dealing with human cases of paraquat poisoning. I know from speaking to Jon that he feels strongly that the case made in the mid-70's was extremely poorly presented and that the data was 'selected' to arrive at a conclusion that 0.05% wt/v should be an inclusion rate of 796.

Happily, I was not involved in the generation of these data, but, of course, I was around when the decisions were being made. I think it most likely that given the pressure at that time to arrive at a decision the apparent omissions in the arguments presented to the Business were accidental. However, given that Jon is very keen to raise this issue I thought it would be helpful if you could read, in detail, Jon's comments and then discuss with me the most appropriate way to put this to bed. I have asked Judith to arrange a meeting between you and me in 2-3 weeks time to discuss this.

Judith Burton

MP Dr L L Smith

From
Dr J R Heylings
Biochemical Toxicology

ICI Central Toxicology Laboratory

Alderley Park
Macclesfield Cheshire SK10 4TJ

To
Dr. L.L. Smith
Head, Biochemical Toxicology

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5.9.90

CONFIDENTIAL

HUMAN DATA WITH THE PARAQUAT EMETIC (PP796)

I have reviewed the data presented on the phosphodiesterase inhibitor PP796 (ICI 63197) in ICI Pharmaceuticals Reports by Farrell, F.G. in 1970 (PH18987C) and Bayliss P.F C. in 1973 (PH 20992C). Clinical trials were performed on this drug in human volunteers as well as in patients with various diseases. It was identified during the course of these trials that a side-effect of the drug was nausea and vomiting in some individuals.

Following studies at CTL in dogs, pigs and monkeys it became clear that PP796 was an effective and reliable emetic agent of considerable potency. As a result, PP796 was chosen in January 1976 as a candidate for addition to the Paraquat concentrate Gramoxone.

It was clearly crucial that PP796 must be added to Gramoxone at an effective concentration in a minimally lethal dose of Paraquat. A report by Dr M.S. Rose (CTL/R/390R) presented a summary of some of the clinical data from the above reports where he gave evidence to support such a concentration. It was suggested that a concentration of 0.05% w.v. (or 5mg in 10ml) PP796 should cause emesis in man within one hour following ingestion of a minimal lethal dose of Gramoxone in the majority of poisoning cases.

I would like to point out that the human data presented in Report CTL/R/390(R) is very misleading. In the attached table, I have presented two sets of data. Data presented by Rose in CTL/R/390(R) is shown at the top. The actual data presented by Bayliss in PH20992C is shown at the bottom.

There are three important differences between the data from CTL/R/390(R) and PH20992C.

1. Data from 2 volunteers dosed with 3mg PP796 has been omitted.
2. Data showing a 4/37 vomit response (from patients with various diseases) at 2mg PP796 has replaced a 0/3 response in the volunteer study on which the rest of the data is based. (Incidentally 4/37 should be 4/1356 dosings or 0.3%.
3. Time to vomit at the top dose of 8mg PP796 which was 2 hours has been completely ignored, yet the author stresses how important it is that emesis occurs within 30 min.

Prediction of a likely ED50 from the human data is obviously very difficult with small group sizes. However, much is known in animals about the steepness of the dose versus onset of emesis curve with the emetic. By normalising "selected data" the percentage vomiting response of 0,11,50,100 following 1,2,4 and 8mg PP796 produces a plausible dose-response relationship. Consequently, this infers that "a dose of 5mg. PP796 in a minimally lethal dose of Paraquat would probably cause emesis in the majority of cases" as suggested by Rose.

However, on examination of the full data there is no such dose response. The minimal effects observed at 4 and 8mg PP796 suggest that 4-8mg doses are probably nearer threshold in man not maximal. Furthermore, the dose response curves in pig, dog and monkey are all very similar across the same dose range. I would suggest that the emetic dose response curve of PP796 in man is similar to these other species. Thus, I disagree with the conclusions in report CTL/R/390 (R), which suggest that the emetic is 10 times more potent in man.

As toxicologists, we are continuously asked to make scientific judgements of risk assessment issues using experimental responses in different species to particular chemicals. In the case of Paraquat and PP796 we are in a unique position of being able to judge responses in man with both chemicals with a good deal of confidence. It appears to me that the above case for choosing an effective emetic dose in Paraquat has not been judged correctly. As far as I am aware (after studying the emetic correspondence files) the human data with PP796 was not questioned during the period 1976/77. Consequently the human dose response data with PP796, reported by Rose, has remained to this day undisputed.

I have documented my findings in this letter since I feel that this issue is extremely important in the impending ICI Agrochemicals Board Paper which is to discuss increasing the level of emetic in Gramoxone. I am fully aware that a 5 fold increase in emetic concentration was recommended in 1985. This followed further observations in the dog with Paraquat and PP796. Our current studies in 1990 are in very close agreement. Thus, the effective dose of PP796 in dogs to produce emesis within 30 minutes is about 0.2mg/kg. Therefore, if man were to respond to the emetic at similar dose levels as the dog, then a minimal lethal dose of Gramoxone (10ml) should contain at least 15mg PP796 or three times the 1976 proposed level.

The whole argument is based on whether or not there are species differences in response to PP796. I think it is extremely unlikely that PP796 is ten times more potent in man compared to pig, monkey and dog as stated by Rose, having reviewed all the data at my disposal.



Dr. J.R. Heylings
Biochemical Toxicology

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 |

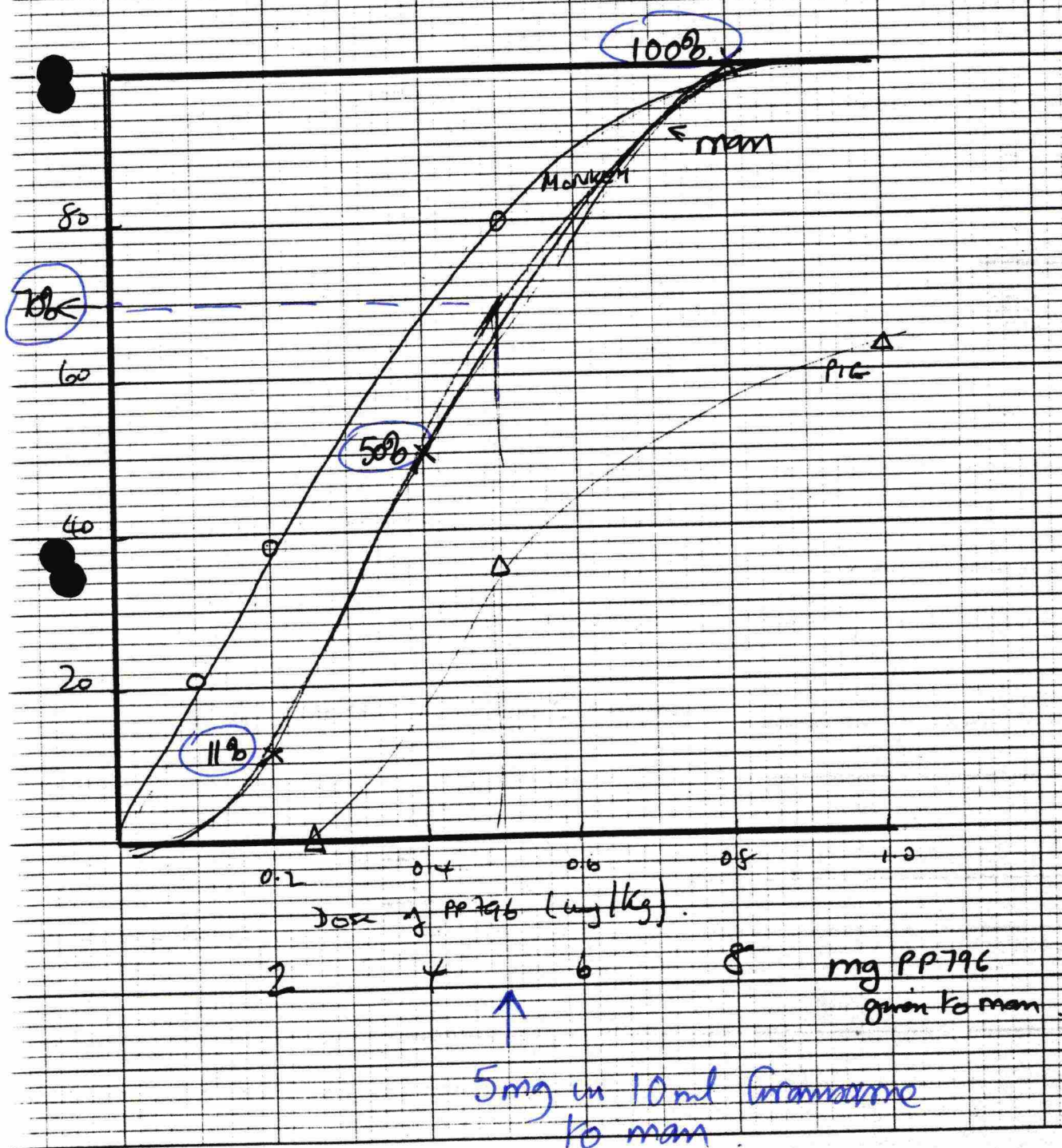
Complete Data from Clinical Report PH20992

| 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 |

Where did 0.5 mg/ml PP796 come from?

CTL/R/390

m.s. Rake. notebook.



From
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To
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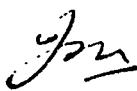
| | | | | |
|----------|------------|---|---|---------------|
| Your ref | Our ref | Direct line | Tel ext | Date |
| | JRH009/LCM | Redacted - EU PII | | 31 January 90 |

EMETIC CONCENTRATIONS IN PARAQUAT FORMULATIONS

Stuart,

To answer your question about the clinical data with the emetic ICI 63197 (PP796), I have studied all the evidence that exists at Pharmaceuticals including a summary report by Bayliss, PFC, PH20992B, 1973. As far as I am aware there is no further data with this compound in man.

The original human study for this Development compound was in 12 volunteers at Dundee in the early 1970s. This study identified nausea at doses of 0.5-8mg PP796 and vomiting in 2 out of the 12 volunteers. All trials subsequent to this were carried out using 2mg PP796 in a further total of 52 patients. The total incidence of vomiting was 7% of individuals receiving a 2mg dose (4/55). However, many of these patients received the compound three times a day for several weeks with no incidence of nausea or vomiting. Since no therapeutic effects were found in the specific disease areas targetted, together with the potential nausea/vomiting side effect, the compound was withdrawn from development. I have discussed this data together with the historical aspects of emetic in paraquat formulations with Lewis and he has agreed to arrange a meeting at Fernhurst to re-visit this issue.


J R HEYLINGS
Biochemical Toxicology

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)

From
DR B COX

To
DR SANDRA ALLEN
CTL

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Copies to
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Mr R Hatton

Your ref

Our ref
BC/LC

Tel ext
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Date
11 Apr 86

Dear Dr Allen,

I have discussed the information that you provided on the Emetic in PREEGLOX with the head of my Cardiovascular Evaluation Laboratory, Mr R Hatton, and would make the following points:-

1. Phosphodiesterase inhibitors such as ICI 63197 are cardiac stimulants both by a direct action and by an indirect effect caused by vasodilation and reduced blood pressure. In Mr Hatton's experience such compounds produce more cardiac stimulation in the dog than in the rat where in the latter case the reduction in blood pressure appears most important.
2. It is a rather large assumption to make therefore that a single p.o. dose of a phosphodiesterase inhibitor, which transiently increases heart rate and cardiac output, will necessarily produce heart muscle damage, particularly when the increase in heart rate can only be demonstrated after i.v. administration.
3. The studies of Naguchi et al., at lethal doses in rats, do not appear relevant to the p.o. route and also have inadequacies in both experimental design and the measurements taken. Thus if their claims were to be justified they should have used other pretreatment groups which included the emetic in the presence and absence of the other additives present in PREEGLOX. A measure of Blood Pressure should also have been included. In any case the direct extrapolation from bolus i.v. injection to the consequences of drug absorbed orally is unacceptable.
4. It is difficult to comment on the studies in man without seeing the data, but these patients (2 out of 8) may have been predisposed to angina (e.g. for equivalent workload and heart rate changes) and in any case angina per se will not necessarily lead to cardiac damage or manifest itself as A-V block as found by Naguchi et al., in their experimental studies. Therefore these findings appear not to be relevant to the case under discussion.
5. From the dog and rat bioavailability data it would seem that ICI 63197 does not have a high bioavailability following oral dosing (e.g. 10 times the effective i.v. dose of 63197 is without effect in the dog and 10 to 40 times the lethal i.v. dose in the rat is also without effect). Thus, as you point out the oral doses used in dog studies generate blood levels that are 15 fold lower than projected levels achieved with i.v. administration.

5. Finally from the data you have provided in primates there appears to have been no problems at doses higher than those given to dogs.

Taking all the above points together it would seem that the concerns raised about the cardiovascular consequences of the presence of emetic in paraquat formulations are at the best premature and at the worst irrelevant.

Barry Cox.

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REPORTS/REVIEWS P. 796
EFFICACY LEVELS

September 1984.

DRAFT

EFFECT OF THE ADDITION OF AN EMETIC TO PARAQUAT FORMULATIONS
ON ACUTE POISONING IN MAN

HART, T. B. and WHITEHEAD, A.

SUMMARY

In an effort to minimise the risk of accidental poisoning by ingestion of paraquat formulations, the manufacturer has added an emetic to the products containing paraquat. The addition was shown in animal models (dog and monkey) to increase the potentially lethal oral dose of paraquat by a factor of 3-5. This survey was designed specifically to examine the effects of this addition on paraquat poisoning in man.

640 cases of paraquat poisoning were reviewed, out of which 230 patients had swallowed the product containing emetic. In those patients swallowing the 'emeticised' product, 97% vomited spontaneously, compared with 65% of a retrospective control group who had swallowed 'non-emeticised' product. The speed of onset of vomiting as a result of the emeticised product was usually within 30 minutes of ingestion.

Comparison of the group of patients poisoning with 'emeticised' product with another retrospective control group involving 'non-emeticised' product shows that the mortality of paraquat poisoning has fallen from 84% to 64% for liquid formulations and from 21.5% to 12% for solid formulations following introduction of the emetic. It is unlikely that improved treatment or smaller doses of paraquat swallowed have caused this reduction, but it is difficult to conclude with any degree of certainty that the emetic addition is solely responsible.

As the emetic has been shown to reduce the toxicity of paraquat in animal models and it is an effective, reliable emetic in man, even in the presence of paraquat, this reduction in mortality of paraquat poisoning may well be due, in part, to the addition of emetic. This addition has not been shown to be associated with any serious adverse effects associated with the use or abuse of paraquat and as it may protect cases of accidental poisoning with paraquat, it is probably better to add emetic to paraquat formulations than to exclude it.

① 230 swallowed emetic. 69 sufficient data to show 67/69 V spontaneously

(64%) 44 V ≤ 30 mins

(95%) 67 V ≤ 60 mins

INTRODUCTION

Paraquat, (1,1 dimethyl-4,4'-bipyridillium) was discovered as a herbicide in the 1950's and first sold as a product in 1962. The most common formulation of paraquat available worldwide is Gramoxone, an aqueous solution containing 200g per litre of paraquat ion. This formulation is now sold in over 130 countries throughout the world. In the United Kingdom, paraquat is also sold as a lower strength solid formulation, Weedol or Pathclear, containing 2.5% w/w paraquat and 2.5% w/w diquat, for use by the amateur gardener.

Although paraquat has been shown to be safe in normal use^{1,2,3,4,5}, regrettably its abuse, associated invariably with ingestion of the product, has been responsible for a number of fatalities. In the United Kingdom, the vast majority of abuse arises from suicide⁶ and the incidence of fatal accidental poisoning remains very low. Nevertheless in order to further minimise the risk of accidental fatality from swallowing, the manufacturer has added several chemicals to the formulations. Two of these, a pyridine-based chemical designed to produce an odour and a blue dye have been added to warn people, who may be about to drink concentrated liquid paraquat formulation. The third is an emetic, which has been added to the formulation as a built in first-aid measure.

Prior to the addition of this emetic, a number of selection criteria had to be met. These included:-

1. The emetic should be sufficiently rapid in action.
2. The emetic must be effective, in the presence of paraquat, in removing toxicant from the stomach and increasing the potential lethal oral dose.
3. The emetic must not interfere with the safety of paraquat to man and his environment, associated with normal use.
4. The emetic must be physically compatible and miscible with paraquat in the formulations and must not interfere with the herbicidal action of paraquat.

codenamed PP796, was chosen as the emetic, because during its development as a drug for obstructive airways disease, it was found to be a very potent emetic in man with a rapid onset of action. A single oral dose of 5mg of emetic in an adult was considered sufficient to cause vomiting. It was also considered preferable as it was centrally acting, as opposed to an irritant or peripherally acting emetic. Irritant chemicals can enhance paraquat absorption across membranes. Finally, it fulfilled all the above selection criteria, particularly the second criterion. In animal models (dog and monkey) the potential lethal dose was increased by a factor of 3-5 fold in the presence of emetic.

As a result, this emetic was introduced into paraquat formulations at a concentration of 0.05% w/v, or w/w equivalent to 5mg emetic in 10ml of Gramoxone or 1.5 sachets of Weedol/Pathclear. Thus the emetic was added at a concentration that would cause vomiting should the minimum potential lethal dose of paraquat formulation be swallowed.

The aim of this paper is to review the information from human cases of paraquat poisoning to determine how applicable the animal data is to man. In particular to assess:-

1. How effective the emetic is, in the presence of paraquat, in causing vomiting in man?
2. What effect, if any, has the emetic had on the mortality of paraquat poisoning?
3. What adverse effects, if any, has the emetic addition had?

METHODS

1. Patient Records

The study involved detailed questionnaire and follow-up of patients in the United Kingdom as described by Hart and Bramley⁶ (1983). In particular, effort was made to determine details of the product involved and whether or not the emetic was present. The latter was achieved by one or more of several methods, including identification of the product label (Figure 1), analysis of the original product for presence of emetic and analysis of the patient's urine for the presence of emetic metabolite.

Analysis of the patient's urine for emetic metabolite is a useful means of confirming emetic involvement, but cannot be used to determine its absence. A negative result may be due to emetic absence, but could also arise in patients who have swallowed low doses of paraquat and emetic, in which case emetic metabolite levels may be undetectable or in patients, whose urine was collected too late. (emetic metabolite is usually undetectable in urine taken after 48 hours of ingestion).

2. Control Group

As this study was conducted after introduction of the emetic into United Kingdom formulations and it is extremely difficult to prove absence of emetic involvement, a retrospective control group of paraquat poisoning cases, not involving the emetic, was used.

3. Analysis

The presence of emetic in the original product was analysed by ■

Urine analysis for presence of the emetic metabolite was done using ■

RESULTS

1. General Statistics

The survey has reviewed a total of 640 cases of proven paraquat poisoning out of which 11 were fatal and 529 non fatal. The majority of these cases (529 of the total) were associated with suicidal ingestion and 11 of all fatalities were suicides. Paraquat poisoning is more common in males, 518, than females 12 and poisoning in children is rare (11 cases, all non-fatal).

2. Emetic Cases

The emetic was confirmed as being involved in 230 cases (36% of the total) and in 78 of these, the emetic metabolite was detected in the patient's urine.

3. Effectiveness of Emetic in Causing Vomiting

Only those patients swallowing more than 10ml of Gramoxone or 1.5 sachets of Weedol/Pathclear were considered. Of the 69 patients, who met the above criterion and on whom sufficient information was available, 67 (97%) vomited spontaneously. Spontaneous vomiting is defined, in this context, as vomiting solely due to ingestion of the product.

Figure 2 illustrates the speed of onset of spontaneous vomiting. The majority of patients (64%) vomit within 30 minutes of ingestion and 94% vomit within 1 hour of ingestion.

4. Effect of Addition of Emetic to Paraquat Formulations on Mortality of Poisoning

Table 1 summarised the mortality statistics for patients who have ingested 'non-emeticised' paraquat formulations. These are considered under two categories - low strength solid formulations (Weedol/Pathclear) and concentrated liquid formulations (Gramoxone/Dextrone). Similarly Table 2 summarises the mortality statistics for paraquat formulations, containing emetic, considered in the same categories as in Table 1.

The mortality rate for poisoning with solid and liquid paraquat formulations not containing emetic is 21.5% and 84% respectively, but for similar formulations containing emetic, it is considerably lower with a 12% and 64% mortality rate respectively.

[Handwritten signature]

TABLE 1

MORTALITY OF NON-EMETIC PARAQUAT ^{Formulations.} POISONING

| | Fatal | Non-Fatal | % Mortality |
|----------------------------|------------|------------|-------------|
| <u>Solid Formulations</u> | | | |
| Weedol | 38 | 131 | 22.5) |
| Pathclear | 1 | 11 | 8.3) 21.5 |
| | <u>39</u> | <u>142</u> | |
| <u>Liquid Formulations</u> | | | |
| Gramoxone | 119 | 18 | 87) |
| Dextrone | 4 | 5 | 44) 84 |
| | <u>123</u> | <u>23</u> | |

TABLE 2

MORTALITY OF EMETIC PARAQUAT FORMULATIONS

| | Fatal | Non-Fatal | % Mortality |
|----------------------------|-----------|------------|-------------|
| <u>Solid Formulations</u> | | | |
| Weedol | 14 | 116 | 11) |
| Pathclear | 5 | 25 | 17) 12 |
| | <u>19</u> | <u>141</u> | <u>28</u> |
| <u>Liquid Formulations</u> | | | |
| Gramoxone | 40 | 20 | 67) |
| Dextrone | 1 | 3 | 25) 64 |
| | <u>41</u> | <u>23</u> | <u>92</u> |
| | <u>60</u> | <u>164</u> | <u>120</u> |

TABLE 3
= 224

(Non-emetic)

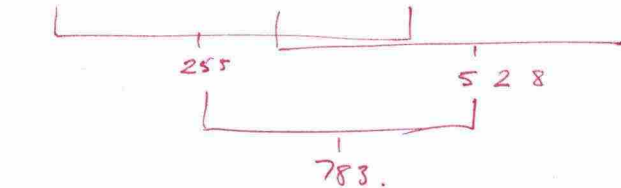
POTENTIAL LETHAL ORAL DOSE OF PARAQUAT (HUMAN)

| Dose of Paraquat Ion Reported as being Swallowed | No Fatal | No Non-Fatal | % Mortality |
|--|-------------|-----------------|-------------|
| <2 g | 10 | 93 | 9 |
| 2-3 to <5 g | 29 | 23 | 56 |
| 5 to <10g | 18 | 2 | 90 |
| 10g or more | 43 | 0 | 100 |
| | <u>100</u> | <u>118</u> | |
| | = 218 | | |

120 / 224 = 53.6%

TABLE 4
PARAQUAT DOSE PROFILE
NON-EMETIC/EMETIC GROUPS

| Dose of Paraquat Swallowed (GM. PQ. ION) | Number of Patients (as % of total) swallowing | | | |
|--|--|--------|---------------------|--------|
| | Solid Formulations | | Liquid Formulations | |
| | Non-Emetic | Emetic | Non-Emetic | Emetic |
| <2 | 81% | 84% | 6 | 15 |
| 2 - <5 | 16% | 15% | 9 | 26 |
| 5 - <10 | 3% | 1% | 25 | 26 |
| 10+ | 0% | 0% | 60 | 33 |
| <hr/> | | | | |
| TOTAL NO OF CASES | 145 | 352 | 110 | 176 |



255

56.

DISCUSSION

The potential lethal oral dose of paraquat in man, has often been cited as 10-15ml of Gramoxone, equivalent to 3g of paraquat ion. We can confirm that this dose is more or less correct by studying doses said to have been ingested by patients. All cases refer to ingestion of non-emeticised paraquat and these are summarised in Table 3. As can be seen, increasing doses of paraquat are associated with higher mortalities. Furthermore, doses of 2 to 5g of ingested paraquat, equivalent to between 10 and 25mls of Gramoxone are associated with about 50% mortality. From the above, we can conclude that the potentially lethal oral dose of paraquat to man is between 2 and 5g of ion equivalent to 10 to 25ml of Gramoxone.

The addition of emetic to paraquat formulations has been shown, using animal models, to increase the potential lethal oral dose by a 3-5 fold factor. If the same is true for man, then the potentially lethal oral dose of 15ml should be increased to approximately 50ml of Gramoxone. Such a dose is rather more than a mouthful (approximately 30-40mls) and should cover those individuals who swallow Gramoxone accidentally. Suicides with paraquat may swallow much more than 50ml Gramoxone and therefore the emetic in these cases is unlikely to be of significant benefit.

The addition of the emetic to paraquat formulations produces a rapid onset of vomiting in the majority of patients (97%) who swallow the product. Paraquat itself is irritating to the gastro-intestinal tract and may produce vomiting. Howard (1979) reviewed 68 cases of paraquat poisoning involving non-emeticised product. About 50-60% of this group vomited spontaneously, but analysis of the original data shows that in 45 cases swallowing more than 10ml of Gramoxone or 1.5 sachets of Weedol or Pathclear, that is similar in doses as the 'emeticised' formulation cases involved, 65% of the patients vomited spontaneously. Hence it can be concluded that the addition of emetic to paraquat formulations has markedly improved the reliability of induction of vomiting. In most cases the addition of emetic has led to an early onset of vomiting.

Comparison of tables 1 and 2 shows that since the addition of the emetic, the mortality of both the solid and liquid formulations of paraquat has fallen from 21.5% to 12% for solid formulations and from 84% to 64% for liquid formulations. The difference in mortality rates between solid and liquid formulations is undoubtedly due to the different concentrations and therefore acute toxicities of the two formulation types. However it is difficult to positively conclude that the reduction in mortality from 84% (liquid) and 21.5% (solid) for 'non-emeticised' formulations to 64% (liquid) and 12% (solid) for 'emeticised' formulations, is solely due to the addition of emetic.

A number of factors will influence the mortality statistics and we have tried to take into account as many of these as possible in forming our conclusions. One factor, which is important, is the treatment given to patients in the 'non-emeticised' and 'emeticised' groups. The treatment for a paraquat poisoning was developed and made available to doctors as early as 1974. Since then it has changed very little. The majority (73%) of the patients in the 'non-emeticised' group occurred after this date, so that treatment is unlikely to be a influencing factor on the mortality rates.

Another possible factor is that the patients in the two groups may have on average swallowed different doses of paraquat. Table 4 shows the type of doses of paraquat swallowed by patients according to the type of formulation involved and whether or not it contained emetic. In the case of the solid formulations, there is very little difference between the two groups, but rather more cases (as a percent of the total) swallowed smaller doses of emeticised liquid formulation compared with the non-emeticised product. It is unlikely that these differences have influenced the reduction in mortality from paraquat poisoning, because the reduction in poisoning mortality with solid formulations containing emetic is far greater (44%) than that involving the liquid formulations (24% reduction).

In spite of the above, it is not possible to account for every influencing factor, and therefore caution must be used when drawing conclusions from the data. However, in view of the fact that the emetic addition has been shown to lower the toxicity of paraquat in animal models and has been shown to cause reliable and rapid onset of vomiting in man, it is likely that this reduction in paraquat poisoning mortality may be due in part to the presence of emetic.

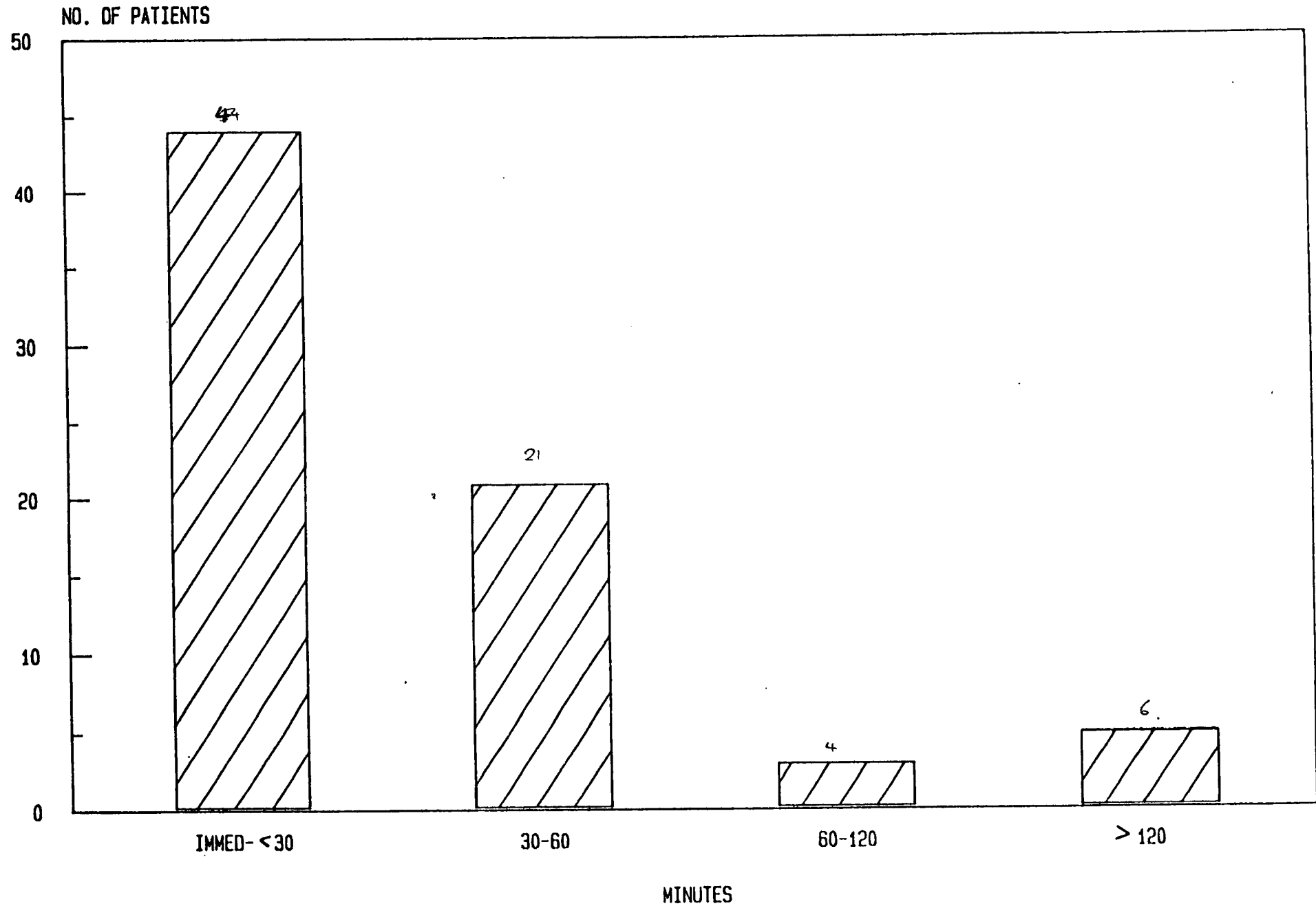
The survey showed very little evidence of serious untoward effects associated with use or abuse of the emeticised paraquat formulations. The occasional instance of persistent vomiting and fluid and electrolyte imbalance was attributed to the emetic, but these were very few in number. Therefore on the basis that the emetic addition may well help protect accidentally poisoned patients with paraquat and is unlikely to be harmful, we believe it is better to have the emetic in the formulations than to exclude it.

TBH/MN
11.9.84.
TBH2

REFERENCES

1. Swann, A.A.B. (1969)
Exposure of Spray Operators to Paraquat.
Brit. J. Ind. Med. 26 322-329.
2. Hearn, C.E.D., and Keir, W. (1971)
Nail Damage in Spray Operators Exposed to Paraquat.
Brit. J. Ind. Med. 28 399-403.
3. Howard, J.K. (1979).
A Clinical Survey of Paraquat Formulation Worker.
Brit. J. Ind. Med. 36 220-223.
4. Howard, J.K. (1980)
Paraquat : A Review of Worker Exposure in Normal Usage.
J. Soc. Occup. Med. 30 6-11.
5. Howard, J.K., Sabapathy, N.W., and Whitehead, P.A. (1981).
A Study of the Health of Malaysian Plantation Workers with Particular
Reference to Paraquat Spraymen.
Brit. J. Ind. Med. 38 110-116.
- * 6. Hart, T.B. and Bramley, A. (1983).
Paraquat Poisoning in the United Kingdom.
Human Toxicology 2 417.
7. Rose, M.S. (1976).
The Effect of Administration of an Emetic (PP796) on Paraquat Toxicity
in Dog and Monkey.
ICI Central Toxicology Laboratories - internal report.
8. Howard, J.K. (1979).
Recent Experience with Paraquat Poisoning in Great Britain.
A review of 68 cases.
Vet. and Human Tox. 21 suppl. 213-216.
9. 'The Treatment of Paraquat Poisoning - A Guide for Doctors'.
ICI Booklet Publication.

EMETIC - SPEED OF ACTION



From: L L Smith

14 September 84

To: Alison Fenna
Bruce Woolen
Mike Godley
I F H Purchase
S E Jagers

LLS/DLB

Please forward comments on this draft document as soon as possible.

L L SMITH

FROM: M J Godley
TO: Dr L L Smith

MJG/KH

cc Mrs A Fenna
Dr B Woollen
Dr I F H Purchase
Dr S E Jagers

25th September 1984

COMMENTS ON DRAFT DOCUMENT ENTITLED 'EFFECT OF THE ADDITION OF AN EMETIC TO PARAQUAT FORMULATIONS ON ACUTE POISONING IN MAN' BY T B HART & A WHITEHEAD

1. There are several cases of apparent differences in 'total' counts of cases. Undoubtedly this is often due to not all the information being available in all cases to enable inclusion in all tables by various factors. However, I feel some comment to this effect might allay fears that the numbers are 'incorrect'. Others may be the result of my misunderstanding the figures in which case perhaps more comprehensive table headings would resolve, eg:
 - a) pg 5 para 2 '230 cases' compared to pg 6 Table 2 with a total of 224 cases.
 - b) Does Table 3 refer to solid and liquid formulation or solid only? Pg 8 line 8 says all cases but total in Table 3 is 218 and in Table 4 145 + 110 = 255.
 - c) Pg 1 para 2 '640 cases' compared to a total of 783 in Table 4.
2. Has the balance of solid to liquid formulation changed (Tables 1 and 2)?
'Non-emetic' (older) cases solid 181 liquid 146 (ratio 1.2:1)
'Emetic' (newer) cases solid 160 liquid 64 (ratio 2.5:1)
Is the identification of formulation containing emetic 'easier' if solid rather than liquid?
3. Table titles 1 and 2 'poisonings' compared to 'formulations'.
4. Should second lowest dose category in Table 3 read '2 to <5g' (not '3 to <5g') as in Table 4? This would correspond with text statement on pg 8 line 6 'doses of 2 to 5g ... associated with about 50% mortality'.
5. I have checked by crude methods the numerical support for some of the statements made ie
 - a) Pg 5 last para: 12% and 64% being 'lower' than 21.5% and 84% - justified.
 - b) Pg 9 1st para: 44% reduction 'greater' than 24% reduction - justified.
 - c) Pg 8 para 3: increased incidence of vomiting 67/69 compared to 45/60 - justified.

6. The paper acknowledges that a number of other factors may influence the mortality data (pg 8 and 9). The references to 'treatment for paraquat poisoning' and possible differences pre-1974, made me interested to know the years applying to the two data bases 'emetic' and 'non-emetic'. The conclusion that differences in 'treatment for paraquat poisoning' are unlikely to be an influencing factor on mortality rates is a little strong. In the case of liquid formulations it is undoubtedly reasonable to assume that this factor could not 'explain' the reduced mortality but in the cases of solid formulations even though 73% of the 'non-emeticised' group occurred after 1974 it is possible (by applying a 47% mortality rate pre-1974 and a 12% mortality rate post-1974 - for both emetic and non-emetic groups)- for the reduced mortality rates observed to have been totally the result of 'improved' treatment.
7. The phrase 'potential lethal dose' is unclear to me. It is not quantitatively defined and appears on pg 8 para 1 to be more related to the incidence of 50% mortality ('2 to 5g ... associated with about 50% mortality') than to what I intuitively expected, ie the lowest dose at which lethality becomes a real possibility. I have difficulty reconciling the statement that 'the potentially lethal dose to man is between 2 and 5 g ...' (pg 8 line 8) when Table 3 clearly shows deaths at doses of <2g. (I acknowledge the uncertainties associated with the dose estimates in this Table.) The implication of the observation that following the introduction of the emetic the potentially lethal dose is '... rather more than a mouseful ...' (pg 8 line 4 para 2), ie that a mouthful is not potentially lethal, seems unconvincing to me.
8. Finally I am concerned about the way in which the data in Table 3 might be abused.

For example assuming dose levels for each category of <2g (say 0.5g), 2g to <5g (say 4g) and 5g to <10g (say 8g) the application of a probit mortality dose-response relationship yields estimates of the human LD50 of 2.8g but more importantly of an LD1% (intuitively a 'potential lethal dose'?) of 0.14g.

I believe the data cannot 'prove' reduced mortality due to the emetic but on balance a reasonable judgement would be that it has made some contribution to this.

*i.e. agrees with
conclusions of the
report.*

M J Godley

M J GODLEY

IMPERIAL CHEMICAL INDUSTRIES PLC

Central Toxicology Laboratory

ANALYTICAL CHEMISTRY SECTION REPORT

FROM: B.H. WOOLLEN

TO: T.B. HART

COMPOUND AND STUDY:

STUDY NUMBER:

COMPOUND NUMBER:

EMERIC PUBLICATION

| <u>Page</u> | <u>Para</u> | <u>Comment.</u> (M.S. = misspelling) |
|-------------|-------------|--------------------------------------|
| 2 | 1 | M.S. <u>aqueous</u> |
| | last | M.S. vomiting M.S. potentiated |
| 9 | 2 | M.S. vomiting |
| | 3 | M.S. emeticised |

Analytical methods: —

product — — by thin-layer chromatography

urine — — by high performance liquid chromatography

(n.b. An acknowledgement of our analytical efforts would be appreciated)

B.H.W.

1.10.84

Paraquat Poisoning in the United Kingdom. A. Bramley & T. B. Hart. Poisons Unit, Guy's Hospital, London SE1 9RT and ICI Plant Protection Division, Fernhurst.

This is an interim report of a study jointly conducted by the National Poisons Information Service at Guy's Hospital, London and ICI Plant Protection Division. It was started in 1980 and has now been running two-and-half years.

The objectives of the study are to:

- 1 Examine in detail the incidence of paraquat poisoning in the United Kingdom.
- 2 Evaluate new and existing treatment methods for paraquat poisoning with particular emphasis on the use of Fuller's Earth and charcoal haemoperfusion.
- 3 Evaluate the effectiveness of an emetic added to paraquat formulations since 1977.

Following extensive media publicity of paraquat's toxicity, the number of paraquat poisonings increased in the period of time from the early 1970s to 1976. Since that year the number of cases, fatal and non-fatal, has remained more or less constant. This study shows that all fatal cases of poisoning resulted from ingestion of paraquat and the majority (95%) were associated with deliberate intent. According to the Office of Population and Censuses and Surveys fatal paraquat poisonings (suicides) now account for 1% of all suicide fatalities and 24% of all suicide fatalities involving chemicals. Accidental fatalities from paraquat poisoning remain very low and account for 0.3% of all accidental fatalities involving chemicals.

The majority of the 262 (fatal 36%, non-fatal 64%) paraquat poisonings over the period reported in this study were male and adult. No children were involved in any fatal paraquat poisoning incidents. There appears to be no reproducible monthly variation in the number of poisonings involving either liquid (for professional users only) or solid (for the amateur gardener) formulations. Where information was available, patients poisoned with the liquid formulations were reported to have connection with the legitimate use of the product, indicating that the Poisons Regulations had not been violated.

Early treatment of paraquat poisoning (up to 12 to 24 hours) appeared to improve prognosis when the dose of paraquat ingested was relatively low. However, it has so far not been possible to demonstrate an improved prognosis associated specifically with the use of Fuller's Earth or gastric lavage. Nevertheless it is recommended that these measures should still be used and at the earliest opportunity.

28 cases of paraquat poisoning were reported as having been treated by charcoal haemoperfusion, but in each case the treatment was carried out only once and for a limited period of time. Similarly there is no evidence so far that perfusion used in this way improves prognosis.

Evaluation of the effectiveness of an emetic addition to paraquat formulations has so far proved difficult owing to the fact that confirming the involvement of emetic is necessary in each case. Nevertheless it has been possible to show that this addition significantly increases the incidence of early spontaneous vomiting. The study will continue to monitor this aspect of paraquat poisoning.

Mortality Rate, Course and Therapy of Paraquat Intoxication. T. Zilker, G. Gerber, G. Mathes & V. Clarmann. Toxikologische Abteilung der II. Med. Klinik rechts der Isar der Technischen Universität München, Ismaninger Strasse 22, 8000 München 80, F.R.G.

Twenty-six patients with paraquat intoxication were admitted to our hospital between 1974 and 1981. In five cases, paraquat intoxication was only suspected (two patients suffered skin contamination, two ingested contaminated food and one contaminated soil). All remained asymptomatic and in none was paraquat detected in the urine. Seven cases were the result of accidental ingestion; four survived, and paraquat was detected in the urine of all but one patient. Two patients were murdered and a further 12 cases were the result of attempted suicide. Only one patient in this group survived (mortality rate in suicide + murder cases: 93%, mortality rate in accidental cases: 43-50%).

Those patients with a fatal course can be divided into two groups: 1 Four patients who died acutely within 8-92 hours after ingestion. The cause of death was irreversible shock, metabolic acidosis and circulatory, renal and hepatic failure. 2 Twelve patients who died within 6-15 days as the result of lung fibrosis. One patient died of cerebral oedema after seven days. All patients had acute renal failure and mild liver damage. Whereas the liver recovered in all those cases who survived for more than seven days, renal function did not always recover completely within this time.

The treatment employed included gastric lavage, haemodialysis and haemoperfusion, steroids, bentonite, inhalation of nitrogen, artificial respiration, gut lavage and superoxide dismutase. In summary, only one patient survived suicidal paraquat intoxication. None of the patients (suicidal + accidental) who survived suffered permanent organic damage (liver, kidney or lung).

ICI PLANT PROTECTION DIVISION

Prepared By: Dr T B Hart

Executive Meeting: 9 January 1984

Submitted By: Dr J T Braunholtz

Date: 3 January 1984

THE ADDITION OF EMETIC (PP796) TO PARAQUAT FORMULATIONS

INTRODUCTION

The objective of this document is to provide an up-to-date review of our current understanding of the effect on toxicity of paraquat formulations of the addition of the emetic, PP796. Included in this review will be a discussion on emetics in general and whether or not the optimum emetic or dose of emetic has been added to paraquat formulations.

EMETICS IN MEDICINE

Most medical practitioners regard the use of emetics with poisoned patients as first aid treatments designed to remove toxicant from the stomach, leaving less available for absorption. They may simply involve mechanical stimulation of the back of throat or the use of more complex pharmaceutical emetics. The addition of the emetic, PP796, to paraquat formulations can therefore be regarded as a built-in first aid measure.

Pharmaceutical emetics fall into two categories depending on their mode of action.

1. Irritant emetics - their action depends on irritation of the stomach lining, with reflex nervous response leading to vomiting.
2. Centrally acting emetics - their action depends on absorption of the emetic into the blood and the effect of that emetic (or metabolite) on chemoreceptors present in the brain stem.

Emetics, such as tripolyphosphates and salt water are classified as irritant emetics. PP796 and apomorphine only exert their effects via a central effect on the brain stem. Finally emetics such as ipecacuahna and copper/zinc sulphate are both centrally acting and irritant emetics. 'Gramoxone' itself is an irritant emetic.

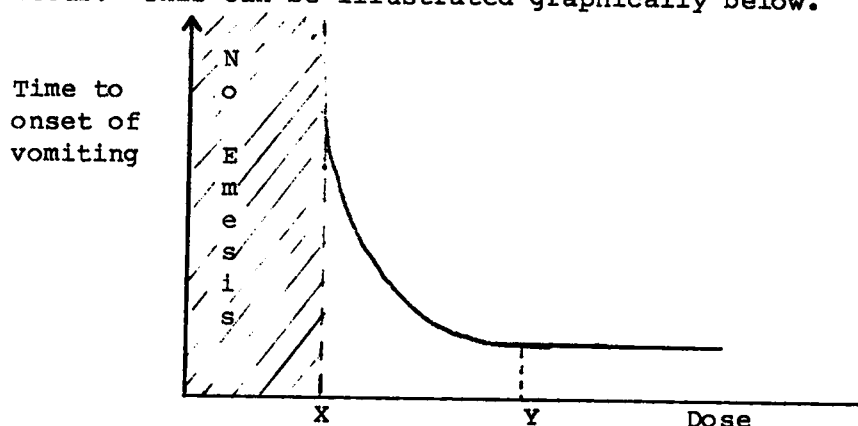
Emetics which have been used or are still used in clinical practice are salt water, apomorphine, copper sulphate and ipecacuahna. Salt water is no longer recommended, because it was found to be too unreliable and toxicity, particularly in children, had occurred. Copper sulphate proved to be a reasonably reliable emetic, but doubts concerning copper toxicity led to it being discontinued as an emetic. Apomorphine and ipecacuahna syrup are still used and the latter is by far the most widely used emetic.

Centrally acting emetics, such as apomorphine will reliably induce vomiting and do so within a few minutes provided it is given by injection. Apomorphine is ineffective by oral administration. Ipecacuanha is not as reliable an emetic in man and has to be given in fairly large doses - 15 - 30 ml of syrup.

EFFECTIVENESS OF EMETICS

There are two criteria by which an emetic's effectiveness can be judged. Firstly whether or not the emetic reliably induces vomiting in any given population and secondly whether or not the emetic will reliably cause an early onset of vomiting. Ideally the effective emetic should cause vomiting in all subjects it is given to and cause vomiting reliably within a few minutes of administration (there is no instantaneous emetic available to date).

It is generally understood with emetics that there is a threshold dose, which once achieved, reliable induction of vomiting will occur. The same may also be true for the speed of onset of vomiting with irritant emetics, but with centrally acting emetics, because many depend on the rate of rise of plasma emetic levels, it is likely that a dose response curve will occur. This can be illustrated graphically below.



It is not known, whether or not dose Y (the minimum dose to cause the fastest onset of vomiting) is the same or greater than the dose necessary to cause reliable induction of vomiting^(X). The route of administration can also confuse the issue. Apomorphine, a centrally acting emetic, will reliably induce vomiting within a few minutes of ingestion, but only when given by intravenous injection. Orally administered centrally acting emetics, such as PP796 need to be absorbed first before there is sufficient plasma concentration rise to affect the chemoreceptors in the brain stem. Thus there is likely to be a wider variation in the dose of PP796 necessary to cause reliable rapid vomiting, than for apomorphine injected directly into the blood stream.

Finally, assuming that the optimum dose of emetic is given in order that reliable induction of vomiting occurs at the earliest opportunity, the overall effectiveness of an emetic in removing toxicant from the stomach depends on several other factors. These include the presence or absence of food/fluid in the stomach or whether or not the patient is resting or ambulant⁽¹⁾.

CHOICE OF EMETIC FOR PARAQUAT FORMULATIONS

In selecting the appropriate emetic to add to paraquat formulations, ICI PPD and CTL believed that a number of important criteria must be fulfilled. These included.

1. Speed and Mode of Action

The emetic must produce a rapid onset of vomiting. A centrally acting emetic was the type of emetic preferred, because an irritant emetic could potentially increase the rate of paraquat absorption. Irritants were known to increase paraquat absorption through skin and other membranes.

2. Effectiveness in Removing Toxicant

The emetic must be able to act in the presence of paraquat and be able to remove enough paraquat to significantly reduce its toxicity.

3. Safety

The emetic addition must be shown to produce no additional hazard to man or the environment over and above the existing potential hazard associated with the use of paraquat.

4. Physical Compatibility

The emetic must be miscible with paraquat in the formulation and must not interfere with the biological action of paraquat.

PP796 had been developed by ICI Pharmaceuticals Division as a drug for treating asthma and related conditions. By the time it reached the stage of clinical trials a considerable amount of animal toxicology on the chemical had already been done. Unfortunately ICI's expectations for it as a drug were short-lived, owing to the fact that it proved to be a very potent emetic agent at therapeutic doses.

In view of its potent emetic properties, and the fact that so much was known about its toxicology, PP796 was almost an automatic choice for the addition of an emetic to paraquat formulations. The fact that it was such a potent emetic also meant that very little PP796 needed to be added to formulations, thereby minimizing any potential adverse effects on the environment. Finally PP796 did fulfill the remaining criteria mentioned above and on that basis, it is considered to be best choice of emetic.

POTENTIAL BENEFIT IN ADDING PP796 TO PARAQUAT FORMULATIONS

Animal studies involving dogs, monkeys and marmosets showed that PP796 addition to paraquat formulations removed sufficient paraquat from the stomach by emesis to increase the potentially lethal oral dose of the product by 300% to 500%⁽²⁾.

In addition to the above, PP796 appeared to confer two other advantages:-

1. Delay in Gastric Emptying

Evidence produced from animal studies showed that

- a) The main site of paraquat absorption was beyond the stomach^(3, 4, 5)
- b) PP796 could delay stomach emptying and thus reduce the rate at which paraquat could be absorbed into the blood^(6, 7)

This, if true for man, would effectively mean that more time would be made available for treatment with gastric lavage and Fuller's Earth. The possibility of buccal absorption is considered irrelevant in the context of poisoning by ingestion, because the retention time in the buccal cavity in such cases is likely to be too short to allow significant absorption to take place.

2. PP796, not only induces vomiting but also causes dizziness, flushing, nausea and makes a patient feel unwell. In many cases these unpleasant side effects may cause the patient to seek medical attention sooner rather than later, thus helping to effect early treatment.

CONCENTRATION OF PP796 FOR PARAQUAT FORMULATIONS

In order to decide upon this, it is necessary to determine the optimum dose of PP796, which will reliably induce vomiting and at the earliest time after administration.

In animal studies (dogs and monkeys), doses in the range 1 - 2 mg/kg bodyweight are necessary to cause reliable vomiting^(8, 9). Man appears to be more sensitive to PP796 than these animals, but there are limited data, owing to the fact that PP796 (originally coded ICI 63197), was developed as an anti-asthma drug and not as an emetic. Doses ranging from 1 mg through to 8 mg were administered orally to human subjects⁽¹⁰⁾. In summary the following results were obtained (Table 1).

Table 1

| Dose | No. of Subjects | % Vomiting | Time of onset of vomiting |
|------|-----------------|------------|---------------------------|
| 1 mg | 2 | 0 | - |
| 2 mg | 37 | 11 | ? |
| 3 mg | 2 | 0 | - |
| 4 mg | 2 | 50 | 30 minutes |
| 8 mg | 1 | 100 | 2 hours |

From the above table it was concluded that 5 mg in man would be the dose necessary to reliably induce vomiting, but it is not known from the above whether or not this dose is the optimum one for causing the earliest possible vomiting. However in animal studies involving paraquat and diquat solutions given to monkeys and dogs^(2, 11), there was no evidence to show that at doses above those causing reliable induction of vomiting (2 mg/kg bodyweight), any increase in dose of emetic reduced the time to onset of vomiting.

The minimum potential lethal oral dose of paraquat in man is considered to be 2 g paraquat ion equivalent to 10 ml 'Gramoxone' or 1.5 sachets of 'Weedol'/'Pathclear' (see Table 6). Based on the above estimate, it was considered that the addition of 5 mg of PP796 to every 10 ml of 'Gramoxone' or 1.5 sachets 'Weedol'/'Pathclear' would be necessary to have an effective emetic dose present in these formulations. The rationale for this decision was summarised by Dr M Rose⁽¹²⁾.

EFFECTIVENESS OF THE ADDITION OF PP796 TO PARAQUAT FORMULATIONS IN CAUSING VOMITING

Paraquat formulations themselves, e.g. 'Gramoxone' will act as irritant emetics. Dr Howard in a review of 68 cases of paraquat poisonings in the United Kingdom⁽¹³⁾ estimated that just over 50% of patients swallowing paraquat formulations will vomit spontaneously. The raw data for this publication has been reviewed and it was found that 60 - 70% (35) of 45 patients, swallowing more than 10 ml 'Gramoxone' or 1.5 sachets of 'Weedol'/'Pathclear', will vomit spontaneously. All these cases involved non-emeticised paraquat formulation.

Since 1979, ICI PPD in collaboration with the National Poisons Information Service have specifically monitored paraquat poisoning in the United Kingdom, with particular emphasis on 'emeticised' cases. From this study, and from other proven 'emeticised' cases in other countries, out of 63 patients studied 60 (95%) vomit spontaneously. The same selection criteria of patients was employed as for above. Where information is available, 'emeticised' cases vomit early (within 30 minutes of ingestion), whereas cases vomiting spontaneously after non-emetic paraquat ingestion do so within a very variable period of time.

EFFECTIVENESS OF PP796 IN DELAYING GASTRIC EMPTYING

The study of human poisoning cases with paraquat cannot show whether or not paraquat has delayed gastric emptying, but it does give information on whether the rate of paraquat absorption has been reduced or not.

The peak plasma concentration of paraquat following ingestion is thought to occur between 0 and 6 hours of ingestion, so that if PP796 delays gastric emptying and reduces the rate of paraquat absorption, the time to achieve peak plasma concentration should be increased. The following table shows plasma paraquat levels in several patients, who have had blood samples taken very soon after ingestion.

Table 2

All these patients have ingested paraquat plus emetic.

| Identity | Sex | Formulation | Dose (Approx) | Estimated Peak Plasma Time | Outcome |
|----------|-----|-------------|---------------|----------------------------|----------|
| MB | M | 'Dextrone' | 70 ml | 0 - 7 hours | Survived |
| MM | F | 'Gramoxone' | 20 ml | 0 - 5 hours | Died |
| DO | M | 'Weedol' | 1 sachet | 0 - 6 hours | ? |
| JI | M | 'Weedol' | <1 sachet | 0 - 6.5 hours | Survived |
| M | M | 'Weedol' | 1 sachet | 0 - 8 hours | Survived |
| EH | F | 'Weedol' | 4 sachets | 0 - 3.5 hours | Died |
| JC | M | 'Weedol' | 1 sachet | 0 - 2 hours | Survived |

Obviously from the above, especially the last two patients, it is clear that the time to achieve peak plasma concentration has not been improved by the addition of PP796. Therefore the argument that delay in gastric emptying, clearly shown in animal studies may benefit cases of paraquat poisoning does not appear to hold true for man. The other significant point emerging from the above table is that if paraquat toxicity is related to peak plasma concentration, then speed of treatment is absolutely essential in order to save a poisoned patient.

EFFECTIVENESS OF PP796 ADDITION IN LOWERING THE TOXICITY OF PARAQUAT FORMULATIONS TO MAN

Since 1979, ICI Plant Protection Division has collaborated with the National Poisons Information Service (New Cross Hospital) in the follow-up of paraquat poisoning cases. In fact ICI pays for the salary of information officer, on contract, to do this follow-up, with particular emphasis on studying cases involving emeticised paraquat formulations. The difficulty in proving the presence or absence of emetic involved in addition to the overall difficulty in monitoring poisoning cases, especially suicides, has meant that adequate data has been limited. Nevertheless this study has answered some questions with regard to the overall effectiveness of adding PP796 to paraquat formulations.

Two types of analyses are used to review this data. The first involves looking at mortality on an overall product basis, which is cruder than the second method as it does not take into account the dose of paraquat swallowed. The second method takes into account the dose of paraquat swallowed, but suffers the drawback of being a subjective assessment of dose i.e. it is the dose said to have been taken by the patient. To overcome this drawback, it is necessary to study relatively large numbers of patients.

1. Analysis on a Product Basis

Table 3 summarises mortality of paraquat poisoning for 4 major products involved and is taken from poisoning cases occurring between 1970 and 1977 i.e. those cases which will not involve PP796.

Table 3

(1970 - 1977 : Non-emeticised product)

| Product | Fatal | Non-Fatal | Mortality (%) |
|-------------|-------|-----------|---------------|
| 'Weedol' | 38 | 131 | 22.5) |
| 'Pathclear' | 1 | 11 | 8.3) |
| 'Gramoxone' | 119 | 18 | 87) |
| 'Dextrone' | 4 | 5 | 44) |

Table 4 similarly summarises mortality data for poisoning cases between 1978 and 1982 involving the same products, but this will of course involve a mixture of 'emeticised' and 'non-emeticised' products.

Table 4

(1978 - 1982 : Emeticised and non-emeticised product)

| Product | Fatal | Non-Fatal | Mortality (%) |
|-------------|-------|-----------|---------------|
| 'Weedol' | 42 | 185 | 18)20 |
| 'Pathclear' | 8 | 26 | 23.5) |
| 'Gramoxone' | 115 | 36 | 77)75 |
| 'Dextrone' | 5 | 3 | 62.5) |

Mortality: ↑
+ Emetic.

Two types of analyses are used to review this data. The first involves looking at mortality on an overall product basis, which is cruder than the second method as it does not take into account the dose of paraquat swallowed. The second method takes into account the dose of paraquat swallowed, but suffers the drawback of being a subjective assessment of dose i.e. it is the dose said to have been taken by the patient. To overcome this drawback, it is necessary to study relatively large numbers of patients.

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Table 5 similarly summarises data, but only those cases involving 'emeticised' products.

Table 5

(1978 - 1982 : Emeticised product only)

| Product | Fatal | Non-Fatal | Mortality (%) |
|-------------|-------|-----------|---------------|
| 'Weedol' | 12 | 69 | 14.8) |
| 'Pathclear' | 3 | 17 | 15) |
| 'Gramoxone' | 31 | 14 | 68.9) |
| 'Dextrone' | 1 | 2 | 33.3) |

From the above tables, it can be seen that mortality rates for 'Gramoxone' have reduced from 84% for non-emeticised product to 66.7% for emeticised product. Similar changes have occurred for the solid paraquat formulations. However due to the multitude of factors, which can influence overall mortality rates, it is difficult to attribute these changes solely to the addition of emetic.

Interestingly a four-fold reduction in bipyridyl content of product ('Gramoxone' versus 'Weedol'/'Pathclear'), which should theoretically increase the potentially lethal oral dose by a factor of four, is reflected in these statistics by approximately a four-fold reduction in mortality (84% and 21% - non-emeticised liquid and solid products respectively : 66.7% and 15% - emeticised liquid and solid products respectively). If it is assumed that this change in mortality rate is solely due to the dilution factor, then the presence of emetic, which also increases the potentially lethal oral dose by a factor of four, should produce a similar reduction. Clearly this is not the case and so if the above assumption is valid, the emetic may have made some improvement to paraquat poisoning mortality, but not as a big an improvement as the animal studies predicted.

2. Analysis on a Dose Basis

Earlier in the document, the statement is made that the minimum potential oral lethal dose of paraquat in man is 2 g paraquat ion (10 ml 'Gramoxone' : 1.5 sachets 'Weedol'/'Pathclear'). The evidence for this statement is derived from reviewing approximately 250 cases of paraquat poisoning (fatal and non-fatal) which occurred between 1970 and 1977. All cases, therefore, did not involve emeticised paraquat formulation. This data is summarised in Table 6.

Table 6

| Reported Dose Of Pq ion Ingested | Fatal | Non-Fatal | Mortality (%) |
|----------------------------------|-------|-----------|---------------|
| <2 gm | 10 | 93 | 9.4 |
| 2 - 5 gm | 29 | 23 | 56 |
| 5 - 10 gm | 18 | 2 | 90 |
| > 10 gm | 43 | 0 | 100 |

The approximate lethal dose in man (oral) is therefore between 2 and 5 gm paraquat ion and so if the emetic were to increase this lethal dose, one might expect the level to be increased to 5 - 10 g or 10 plus g, (equivalent to 25 - 50 ml 'Gramoxone' or more than 50 ml 'Gramoxone' respectively).

Table 7 summarises the dose comparison involving emeticised formulations.

Table 7

| Reported Dose Of Pq ion Ingested | Fatal | Non-Fatal | Mortality (%) |
|-------------------------------------|-------|-----------|---------------|
| <2 gm | 11 | 71 | 13 |
| 2 - 5 gm | 9 | 16 | 36 |
| 5 - 10 gm | 11 | 6 | 65 |
| > 10 gm | 28 | 1 | 97 |

Comparing the mortalities of the four categories in Tables 6 and 7, it can be seen that there is an improvement in mortality in those people ingesting either 2 - 5 g paraquat ion (56% mortality without emetic versus 36% mortality with emetic) or 5 - 10 g paraquat ion (90% mortality without emetic versus 65% mortality with emetic). The question that is important though, is by how much is the potential lethal dose of paraquat increased in the presence of emetic? Statistical analysis of the data (see Appendix) indicates that the addition of emetic improves the potentially lethal oral dose by about 15% (cf 300 - 500% predicted from animal models). Therefore the conclusions from this analysis tend to concur with the conclusions from the previous analysis on overall mortality, in that the emetic may have made some improvement, but not as much as the animal studies predicted.

CONCLUSIONS

It is evident from the human poisoning statistics, that the presence of emetic in paraquat formulations has reliably induced vomiting in those patients ingesting more than a minimum lethal dose. This suggests that the optimum concentration of emetic has been added to paraquat formulations to reliably cause vomiting, but it is not known whether the optimum concentration is present to cause the earliest possible vomiting.

To answer this latter question accurately, it would be necessary to conduct some human volunteer study, which would involve different emetic doses and monitoring of the time to vomit. I believe such a study cannot be justified for several reasons, including.

- i) To administer a known noxious agent to healthy human volunteers could be considered unethical. Dr Howard on two occasions, and the author on one occasion have approached ICI Pharmaceuticals Division about this and on each occasion a negative view prevailed.
- ii) In explaining the nature of PP796 to volunteers, the problem of autosuggestion would occur. Volunteers receiving a dummy pill as controls may vomit spontaneously simply because they believe they are receiving an emetic.
- iii) Such a study would only give information on time to vomit when PP796 alone is given. It is necessary to know how PP796's emetic properties with regard to time to onset of vomiting would be affected by the presence of paraquat.

It may be possible to determine whether increasing doses of PP796 in man will reduce the time to onset of vomiting, by studying the time to onset of vomiting in poisoning cases who have swallowed different amounts of paraquat and therefore different doses of emetic. Work is now in hand to determine whether or not it is possible to answer the question by this means.

The addition of emetic appears to have had no significant effect on the rate of absorption of paraquat in man and it is recommended that this argument of delayed gastric emptying is no longer used to support the inclusion of emetic in paraquat formulations.

The addition of emetic to paraquat formulations appears to have made some improvement to overall mortality and has increased the potential lethal oral dose in man. It is very difficult, however, to quantify by how much the presence of emetic has increased the potential lethal dose of paraquat. Analysis of mortality rates on a product basis and on a dose basis indicates that this increase is relatively small, certainly much smaller than the increase predicted by animal toxicity studies.

The reason for this may be that animal studies tend to optimize the chances of producing beneficial effects, whereas in practice it appears that these optimum conditions rarely occur. Although the practical significance of addition of emetic remains doubtful, it could be argued that when optimum conditions occur, the maximum potential benefit the emetic could achieve would be a 3 - 5 fold increase in the potentially lethal dose. There still exists, therefore, the justification for continuing with the emetic as it may do some good and is unlikely to be harmful.

Follow-up of paraquat poisoning still continues within the United Kingdom and more data concerning the emetic will be generated. It is doubtful whether the present position on the emetic will change, but it is clear that fatal accidental poisoning with paraquat is becoming an increasingly rare event. Preventative measures such as addition of blue dye and stench, together with labelling and publicity may have contributed to this. I believe the emphasis should be on prevention, particularly in the developing countries.

REFERENCES

1. Walter D. et al (1980) - Vet. and Human Toxicology 22 No. 4 225-234
2. Rose M.S. (1976) - CTL/R/391
3. Daniel J.W. and Gage J.C. (1966) - Brit. J. Ind. Med. 23 133-6
4. Smith L.L. et al (1974) - BMJ 4 1974
5. Bennett P. et al (1976) - Proc. BPS 294
6. Wright A.G. et al (1979) - CTL/R/489
7. Cobb L.M. et al (1979) - ICI/119/78556
8. Farrell F.G. (1970) - ICI 63197 - Submission of Evidence to the Committee on the Safety of Drugs
9. Todd A.H. (1977) - The Emetic Effects of ICI 63197 in Pigs, Monkeys and Marmosets - PH23516C
10. Bayliss P.F.C. (1973) - A Summary of Clinical Results of the Phosphodiesterase Inhibitor ICI 63197 in a Variety of Disease States PH20992B
11. Cobb L.M. et al (1978) - The Effects of the Emetic PP796 on the Oral Toxicity of Diquat in Cynomolgus Monkeys CTL/C/576
12. Rose M.S. (1976) - CTL/R/390
13. Howard J.K. (1979) - Vet. and Human Toxicol. Vol. 21 p 213-216

From

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To

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APPENDIX

RECEIVED

- 3 JAN 1984

PSRG
FERNHURST

Your ref

Our ref

Tel ext

Date

TMW/9/PPS/LB

Redacted - EU PII 3

1 Sept 83

PARAQUAT POISONING STATISTICS - UK

I have considered the data you supplied in your letter of 22 August and where appropriate made statistical comparisons. However, before I would be willing to see my results widely published outside the Company, I would wish to discuss some of the selections and decisions you have made in compiling your figures.

The figures in your Section 1 can be summarised as percentage survivors as follows:

| | | | | |
|-------|-------|------|------|------|
| 1978 | 1979 | 1980 | 1981 | 1982 |
| (57%) | (40%) | 50% | 54% | 67% |

The first two figures are in brackets due to no total number of cases being known. The other figures apply only to known survivors. A direct comparison of 1982 and 1981 values was actually statistically significant at the 5% level. However, this is a very simple approach whereas it could be argued that the data must be considered as a whole. In this case, there are a range of options but it is unlikely that you could so firmly establish 1982 as being an outlier in the context of the 5 years data or that there is a trend.

In relation to section 2.2, I confirmed statistically that there was no evidence of a sex difference in survival; this is fairly obvious since the figures are 67% and 72% for males and females respectively. However, this makes no allowance for differences in dose consumed or in product type used.

Sections 2.3 and 3.1 quite clearly as you state, demonstrate an effect due to product type used. In addition your data i) and iii) can be used to compare the effect of emetic allowing for product type. This summarises (percentage fatal) as:

| | No Emetic | Emetic |
|----------------|-----------|-------------------------------|
| Weedol Type | 22% | 17% |
| Gramoxone Type | 84% | 69% (NB error in your figure) |

Statistical analysis of this table gives a statistically significant effect for addition of Emetic.

The data of tables iv) and v) might also be expected to give a sensitive comparison since allowance can be made for dose ingested. You have naturally summarised this data so that I did not have the actual estimated doses. This is potentially more important for the high and low dose groups. I have carried out two analyses; one assumed doses of 1.0, 3.5, 7.5 and 12g Pq ion for the four groups respectively and the other assumed 0.5, 3.5, 7.5 and 15g. The analysis fits a dose response curve to the mortality, compares the curves of the two data sets to see if they are similar and, based on the assumption that the curves are similar, estimates relative potency. (Relative potency is the ratio of doses required for equivalent effects). Naturally the two analyses produced different results. Whether either or neither is appropriate depends on the appropriateness of the dose assumptions made, they should not be thought of as extremes which cover the range of possible outcomes. The results of the analyses generally suggested some doubts about the model used to analyse the data but not sufficiently that the results have no value. The estimated potency values obtained were 0.83 or 0.85 (emetic/no emetic) but these values were nowhere near significantly different to a ratio of 1.0 ie no difference. As crude estimates however, they remain valid suggesting that the effect of adding emetic is to reduce the effective ingested dose by about 15%.

Clearly the different analyses I have carried out are not independent since they are based on tables which are just different ways of looking at the same information. In theory it is possible to allow for the many aspects such as dose, sex, product type, etc, simultaneously. Whether this data warrants further such examination will depend on the quality of the individual data as well as the interest in the outcome. At present the results are at least encouraging in the sense that addition of emetic seems likely to have had some effect.

216/83

IMPERIAL CHEMICAL INDUSTRIES
Plant Protection Division
Fernihurst Haslemere Surrey
England

PP796

EMETIC AGENT FOR

'GRAMOXONE'

ALW/CVM
ZB88

INTRODUCTION

'Gramoxone' is one of the most widely used herbicides in world agriculture. Since its introduction in 1962 it has established a firm record of effectiveness, and, when used as recommended, of safety.

As a consequence of its record as a useful weedkiller 'Gramoxone' has become readily available throughout the world through many points of distribution. Familiarity with the product has regrettably often led to it being decanted from its original bottle and being stored in drinks containers.

This malpractice has resulted in the accidental deaths of a number of innocent persons who have drunk the contents of a bottle believing it to contain innocuous material. The publicity given to those relatively few incidents have led to the use of 'Gramoxone' as a suicide agent and deaths by suicidal ingestion now far outweigh those resulting from accidental drinking.

ICI was naturally concerned at this misuse of one of its products, albeit in conditions beyond agronomic practice. The Company therefore set up a team, comprised of members of its Plant Protection Division and Central Toxicology Laboratory, to undertake an extensive programme of evaluation and research to seek formulation changes to improve the safety of 'Gramoxone'.

FORMULATION SAFETY : MAIN CONCEPTS

The approach to a safer formulation was considered in two principal ways. The first was to alert people to the fact that 'Gramoxone' is not to be drunk. This could be achieved either by making the product unacceptable if drunk, or by incorporating a warning into the presentation of the product (eg appearance, smell) which would dissuade people from drinking it. However, it was considered that these proposals would not be sufficiently effective in deterring the suicidal use of 'Gramoxone', or in accidents.

The second was to find a compound which could be added to 'Gramoxone' and which would, if swallowed, counteract the effect of paraquat. This could act either as an antidote or as an emetic.

Of the many ideas considered by the research team, the most viable seemed to be the addition of an emetic to 'Gramoxone'. If effective an emetic would be an ideal safety additive which would hopefully cover all situations, children or adults, accidents or suicides.

THE EMETIC CONCEPT

To be of value, the emetic would have to satisfy a number of important criteria.

- a) It must act quickly (within 30 mins) to inhibit absorption of paraquat.
- b) It should be centrally acting and non irritant; any irritancy could increase the rate of paraquat absorption.
- c) It would have to be effective in the presence of paraquat.
- d) It should be toxicologically acceptable and harmless to the user of 'Gramoxone' and to the environment.
- e) It should be stable in 'Gramoxone' and not inhibit the products biological performance.

During the period from 1972 to 1976 an appraisal of existing emetics by ICI's Toxicological Laboratory failed to reveal any compound which would satisfy the criteria listed above.

The principle emetics considered and their reasons for rejection are as follows:

1. Apomorphine

This compound is not orally active and is unstable in air.

2. Matricaria

Insoluble in paraquat.

3. Heavy Metal Salts, eg copper, antimony

These were rejected on toxicological grounds and because they were unacceptable environmentally.

4. Mustard and Oil of Mustard

Mustard is insoluble in paraquat. Oil of mustard, the active principle of mustard is a skin irritant and experience suggests that an irritant would increase the risk of dermal absorption of paraquat.

5. Ipecacuanha

This compound is stable in air and soluble in paraquat but in experiments undertaken on monkeys has been found to be unpredictable in response, slow acting, and at the rate at which it is effective it also causes toxic symptoms. Its emetic action is due to its irritant effect which could increase the rate of paraquat absorption.

THE DISCOVERY AND DEVELOPMENT OF PP796

During 1976, ICI's Central Toxicology Laboratory became aware of the existence of a triazolo-pyrimidine, at one time under development by the Pharmaceutical Division of ICI for the control of asthma. This compound, now coded as PP796 had undergone substantial toxicological investigation and had been granted a clinical trials certificate by the Committee for the Safety of Medicines in Great Britain. During these trials it became clear that PP796 was an emetic agent of high potency in humans. For this reason it was withdrawn from future development as a drug but ICI's Toxicology Laboratory matched its properties against the criteria deemed essential for an emetic for 'Gramoxone'.

Clearly any experimental data in conjunction with paraquat could not be obtained on humans. The results presented in summary below derive for the large part, from studies in monkeys performed by Huntingdon Research Centre. It should be noted that rodent species do not vomit and are therefore unsuitable for the evaluation of emetic agents.

PP796

1. Emetic Response

PP796 is rapidly absorbed following oral administration, peak blood levels being seen in man 30 minutes after dosing. In a study to determine vomiting response in the cynomolgus monkey, five of a group of seven animals vomited several times in less than 30 minutes, the remaining two within 1 hour of dosing. The sensitivity to PP796 as an emetic agent is species dependant. The following table summarises the minimum doses required to produce a 75% vomiting response.

| Species | Dose for 75% response mg/kg |
|---------|-----------------------------|
| Dog | 1.5 |
| Monkey | 0.5 |
| Pig | 1.0 |
| Man | 0.1 |

From this it can be seen that man is particularly responsive to the action of PP796, making this compound the most potent orally effective emetic currently available.

2. Efficacy in the Presence of Paraquat

The vomiting action of PP796 is unaffected in paraquat formulations. It was found that PP796 can, by its emetic action, inhibit the lethality of paraquat to monkeys. The following table provides the results from a typical study in which paraquat with and without PP796 was administered to macaque monkeys.

| No. of animals | Paraquat mg/kg | PP796 mg/kg | Survival |
|----------------|----------------|-------------|----------|
| 8 | 100 | - | Nil |
| 8 | 100 | 2 | 6 |

The mean peak plasma levels of paraquat in the PP796 treated group, including the animals which died, were only 8% of that of the controls.

A further experiment in monkeys in which the doses of paraquat and PP796 were increased showed that the emetic response was capable of effectively changing the lethal dose by a factor of nearly three-fold. The data for this experiment are summarised in the following table.

| No. of monkeys | Paraquat mg/kg | PP796 mg/kg | Survival |
|----------------|----------------|-------------|----------|
| 2 | 100 | 2 | 2 |
| 2 | 250 | 5 | 2 |
| 2 | 300 | 7 | 0 |
| 2 | 500 | 10 | 0 |

3. Safety

PP796 underwent extensive toxicological investigation in the course of its development as a potential drug. The results of these studies, which relate to acute, chronic, teratogenic and carcinogenic effects; were all favourable and have been submitted to regulatory authorities as part of the procedure for the registration of 'Gramoxone' formulations containing PP796.

In addition at the concentration used in 'Gramoxone' (0.05%) PP796 poses no hazard to users of the product. This has been demonstrated in practice by monitoring the use of the new formulation and the absence of any adverse report from the numerous countries in which it is now being sold.

The fate of PP796 in soil and water has been determined using radio-labelled material. In soil, PP796 becomes increasingly bound with time whilst in water, under conditions of sunlight it degrades with a half-life of approximately four days.

After dilution for spraying the effective concentration of PP796 will be 5 ppm which at the highest recommended rate for 'Gramoxone' (8 l/ha) is equivalent to 4 g/ha. This very small amount of material reaching the soil is unlikely to have deleterious environmental effects.

4. Stability

PP796 is completely stable in 'Gramoxone' under all normal conditions of manufacture, formulation and storage.

5. Effect on 'Gramoxone' Performance

Field trials show no effect upon the herbicidal activity of 'Gramoxone'.

Having established the satisfactory matching with desired criteria it was proposed that PP796 be added to 'Gramoxone' at a concentration of 0.05% w/v. This figure is based upon an estimated lowest lethal dose of 10 ml and an effective emetic dose of PP796 to man of 5 mg.

ADDITIONAL PROPERTIES

During the course of investigating the pharmacological properties of PP796 it was suspected that this compound has a delaying effect upon gastric emptying. As most of the absorption of paraquat is from the gut this property could, if confirmed, have practical value.

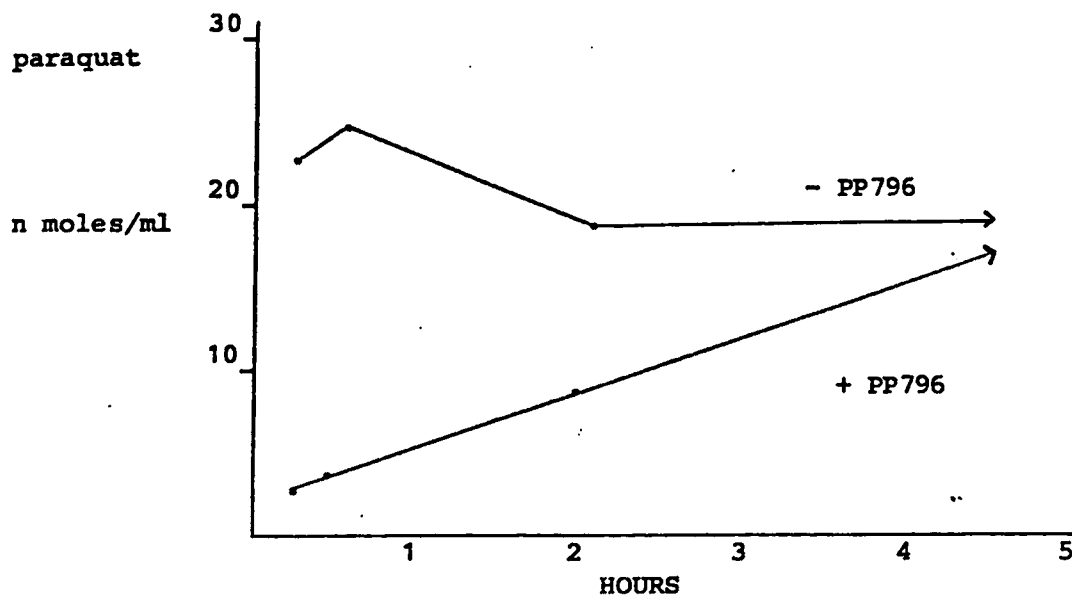
Using marker substances such as phenol red or ⁵¹Cr this delay has been quantified in a number of species as shown in the following table. The delay is expressed as percentage inhibition of passage of a marker substance through the stomach in 1 hour compared with controls.

| Species | Dose PP796 mg/kg | Inhibition % |
|---------|------------------|--------------|
| Mouse | 2.5 | 91 |
| Rat | 0.1 | 37 |
| Rat | 1.0 | 68 |
| Monkey* | 0.2 | 61 |

*The dose used in the monkey was sub-emetic

The practical value of this property, in terms of its effect upon the absorption of paraquat was further investigated. Rats were dosed simultaneously with low levels of PP796 and with paraquat. The plasma paraquat levels achieved, compared with those in a control experiment without PP796 are shown in the graph below.

Paraquat Plasma Levels



It is believed that this additional property of delayed gastric emptying will play an important role in the period immediately following a poisoning incident. In addition to a vomiting reaction reducing the total body content of paraquat, inhibition of its uptake into the blood stream will support the paraquat treatment methods which ICI will continue to recommend.

SUMMARY

The principle of adding an emetic to 'Gramoxone' is seen as an effective step towards reducing fatalities following its ingestion when allied to the treatment already recommended by ICI. Whilst there is no guarantee that this step will be of benefit in those instances of suicide where gross quantities of 'Gramoxone' are consumed, the technical basis for the effectiveness and safety of this measure is strong.

The number of cases of accidental death due to 'Gramoxone' is so low that it will be some time before the benefits of PP796 can be statistically demonstrated. It is nevertheless recognised as an important innovation in many countries, in some of which the presence of an emetic agent in paraquat formulations has been made a mandatory requirement.

October 1976

Oct 1976

Contains original Report by ms Rose as appendix.

P2

COMPANY SECRET

EDC Paper No 729

EMETIC FORMULATION OF PARAQUAT:
PROPOSED STRATEGY FOR INTRODUCTION WORLDWIDE

Author: P Slade

Approved by: T C Frears

Submitted by: A J Maier

SUMMARY

The technical development work with emetic formulations of paraquat is nearly complete and provides assurance that the formulation is less likely to cause death if swallowed and will not result in any additional hazards to users, consumers of treated crops or the environment. The formulations and the emetic agent PP796 have very strong patent protection.

Production of PP796 at Pharmaceuticals Division is proceeding very satisfactorily and regular supplies can be provided from March 1977. Registration of the new formulations is believed to be possible for some key countries in 1977, with virtually all others following in 1978. A publicity announcement about the new formulation is unlikely to be necessary before early in 1977.

The implications of adding stenching agent to paraquat for all markets are examined and the need to assess possible market reactions to a stench product prior to launch in less advanced markets is discussed.

RECOMMENDATIONS

- 1 The action outlined in the report should be taken to enable the emetic formulation to be marketed worldwide as soon as possible - by early 1978 in most countries.
- 2 The registration petition should be submitted to the UK authorities at the beginning of November.
- 3 Other countries where introduction should be sought in 1977 are all the countries of Western Europe, Australia, New Zealand, Malaysia, Indonesia, Japan, Brazil and South Africa. Immediate introduction in Western Samoa should be arranged, with existing stocks of Gramoxone in the country being reclaimed as far as possible.
- 4 PP796 should be incorporated into Weedol, Pathclear and paraquat mixtures with residuals as soon as practicable.
- 5 Overseas companies not yet fully informed about the emetic formulation should be briefed about it as soon as possible.
- 6 Overseas companies should commence discussions with registration authorities as soon as it is appropriate with the objective of seeking to ensure that the emetic is the sole paraquat formulation allowed to be sold.
- 7 Pharmaceuticals Division should be requested immediately to begin production of PP796 at the rate of approximately 1 tonne per month from March 1977.
- 8 Discussions with Pharmaceuticals Division about the price of production quantities of PP796 should take place at the end of November.
- 9 As far as possible, PP796 should be added to paraquat formulations and concentrate at Mond Division (or Yalding). However there will be many exceptions to this general rule; for patent reasons overseas formulations will be worthwhile in many cases.
- 10 The cost of PP796 to PPD should be passed on to the overseas companies, but efforts should be made to prevent further mark-ups being made on the cost by our agents.
- 11 A publicity statement about the new formulation should be prepared as soon as possible with a view to releasing it in the UK and Eire at the time of launch. No publicity announcement would be made outside those countries.
- 12 User trials with stench product overseas and investigation of the possible permeation of stenching agent through non-ICI packs should be carried out by early 1977 to enable recommendations to be made about countries in which the emetic product should also be stench.

THE TECHNICAL CASE

Although the addition of an emetic agent to Gramoxone has been considered in the past as a means of safening the product it had not been pursued because it was believed that no suitable emetic agents were available. The situation has changed dramatically this year with the discovery of PP796 which seems to have all the properties needed in an emetic agent to be added to paraquat formulations.

These properties are:

- i That it will produce rapid and effective vomiting in man at low concentrations and with no adverse side effects. It is believed that this will greatly reduce the risk of death following ingestion of paraquat.
- ii That it is stable and will not affect the physical or chemical stability of paraquat formulations.
- iii That it will not adversely affect the herbicidal action of paraquat.
- iv That it will not give rise to any adverse toxicological or environmental effects.
- v That it will not result in too great an increase in the cost of Gramoxone.

PP796 was developed by Pharmaceuticals Division between 1968 and 1972 as a potential drug for the relief of asthma. Toxicological studies in mammals were completed to the satisfaction of the UK Committee for the Safety of Medicines, which granted a Clinical Trials Certificate. On the basis of this Certificate, trials on humans were carried out in the UK. It became clear from these trials and from data generated in monkeys and dogs that PP796 was an effective and reliable emetic agent of considerable potency.

The rapidity of action and acceptable toxicological characteristics of PP796 give it an advantage over other known emetics and it was chosen, in January 1976, as a likely candidate for addition to Gramoxone. Since then, a programme of work has fully confirmed the preliminary hopes, and is satisfying all the criteria necessary for the acceptance of PP796 as an additive to Gramoxone on a commercial scale and to meet the demands of registration authorities of any country in which it is decided to sell such a product. A summary of the important results obtained to date and of work in progress and projected are set out below.

1 Level of Addition

It is clearly crucial that PP796 should be added to Gramoxone at the right concentration. We are fortunate that results of exposing people to the compound are available from the clinical trials which enables this

level to be set. The concentration that has been selected is 0.05% w.v, ie 5 mg in 10ml of Gramoxone. This is expected to produce vomiting within 1 hour in the majority of those ingesting such a quantity, which is the approximate minimum lethal dose of Gramoxone in man. In fact most paraquat poisoning cases result from the swallowing of 20ml or more and many suicide cases drink 50ml or more.

The use of a 0.05% concentration has the full support of Dr M S Rose of CTL and Dr J T Nicholls of the Clinical Research Department, at Pharmaceuticals Division. A paper by Dr Rose summarising the evidence for this rate of addition appears as Appendix 1.

Consideration has been given to carrying out additional work with humans to establish with greater certainty that the chosen concentration is the correct one. It has been concluded that this is neither practicable nor necessary.

2 Effectiveness in the presence of paraquat

Animal experiments have demonstrated the effectiveness of PP796 in the presence of paraquat. Dogs were dosed with paraquat at a level that killed three out of four animals within four days. All animals in a second group, given the same dose of paraquat plus PP796, vomited within 1 hour and paraquat blood levels were reduced. There were no deaths. Similar results were obtained with monkeys.

Further work has substantiated these findings. The toxicity to dogs of paraquat in the presence of an emetic dose of PP796 has now been estimated to be lowered by a factor of 5, and to monkeys also by a factor of 5, compared to paraquat alone.

3 Toxicology of PP796

Extensive toxicological work was done by Pharmaceuticals Division including acute oral and intravenous toxicity in rats, mice and rabbits, 90 day tests in rats and dogs, teratogenic studies in rats and rabbits and dermal studies in rabbits and guinea pigs and in man.

Further observations have since been made, including toxicity to fish, and acute oral, dermal, irritation and inhalation studies with the pyridine base stented emetic formulation are in progress. PP796 is rapidly absorbed, metabolised and excreted in rats, dogs, monkeys and man.

4 Formulation

Paraquat concentrate, Gramoxone (stented and unstented) and Gramoxone S can be formulated with PP796 and storage tests show that there will be no physical or chemical problems with these products. PP796 can be added to appropriate formulations in pyridine bases, valeric acid (for stented products) or propylene glycol (for unstented product or concentrate)

although work with the latter is incomplete. Systems can therefore be devised for the addition of PP796 to any paraquat product. Stability work and animal studies with paraquat mixtures with residuals, and formulation work with Weedol and Pathclear to enable emetic Weedol to be made at Yalding are in progress or are to be started shortly.

5 Herbicidal Activity

PP796 has been shown, in glass house tests, to have no herbicidal properties.

It is virtually inconceivable that the addition to Gramoxone of PP796 at the low rate of 0.05% would have any adverse affect on the herbicidal activity of the product. This has been confirmed in a series of field tests, in which rates of addition of PP796 of up to 0.2% were examined.

6 Possible hazards to operators

PP796 is not absorbed through intact skin and has low volatility. It has a very short persistence in man. These facts, coupled with the extremely low level of PP796 in spray-strength material virtually eliminates any risk of operator hazard. Observations are now being made in the field on farm workers in the UK spraying stench or stench emetic product as part of the large-scale development. The results obtained so far have not shown any adverse effects from the emetic, although some operators have claimed some minor ill effects from the stench formulation.

Consideration has been given to carrying out trial work overseas to ensure that no side-effects occur when the new formulation is applied from a knapsack sprayer under tropical conditions for several days continuously. Dr Howard, the Division Medical Officer, has concluded after considering all the available data, and taking into account the negative results from the UK trials, that such work will not be necessary.

7 Possible environmental and food residue hazards

When Gramoxone containing PP796 is used in agriculture only about 2g of the compound will be applied per hectare. This low rate of application provides a fair degree of assurance that its residues will not be detectable in food crops and that no environmental hazards will ensue. Work is in progress to confirm this.

A residue method sensitive to 0.01ppm has been developed and has been used to demonstrate absence of residues of PP796 in potato tubers harvested after haulm desiccation with the emetic formulation, and to show that PP796 is degraded on the surface of leaves (probably photochemically).

Preliminary results indicate that the compound is not degraded to any significant extent in soil in periods up to 5 weeks, although it is broken down by sunlight in water.

Work on environmental degradation of PP796 is continuing and an assessment of the significance of its apparent soil stability is being made.

Taint tests with potatoes harvested after spraying with the new formulation were negative.

PATENTS

A UK patent application, disclosing emetic herbicidal compositions comprising a bipyridylium herbicide and PP796 or a close analogue, was filed on 15 April 1976. This case will be completed in the UK and filed in most countries overseas early in 1977, claiming priority under the International Convention. Foreign filings have already been made in the USA (to serve as a basis for claiming priority in some South American countries not members of the International Convention), Taiwan, South Korea and Columbia.

These patents, when granted, should prevent manufacture, import, sale or use of the patented formulations by competitors.

PP796 is protected as a new compound per se by the Pharmaceuticals Division original filing on the compound (UK patent priority 13 September 1968) which also protects the processes of manufacturing. This patent is filed in 24 countries.

The prospects of preventing competitors selling emetic formulations of paraquat seem good, since there will be very few places where they would be free to sell the product without challenging ICI's patents (China, Indonesia, Thailand are the most significant exceptions). There are provisions in the laws of many countries that patents which are not "worked" locally may lapse, or be the subject of compulsory licences. However, in the present case, it should be possible to "work" the invention by local formulation in significant countries.

The prospects of our competitors discovering suitable emetic agents as alternatives to PP796 must be very remote. In any case we have filed patent applications in the UK on mixtures of paraquat with known conventional emetics such as ipecacuanha and mixtures of paraquat with other active emetics discovered by Pharmaceuticals Division. A case covering other pesticides mixed with PP796 has also been filed. A decision to proceed with these cases has not yet been made.

STENCHED FORMULATIONS

The decision was made recently that as a general policy Gramoxone should be stenched, although if a suitable case could be made, individual countries could be exceptions to this general rule.

Discussions have taken place with Regional Marketing Departments on the implications of this decision. It has been concluded that a necessary preliminary to its implementation should be a field evaluation of the presently favoured stenching agents to determine possible adverse reactions amongst field workers in less advanced countries. The form and possible location of suitable trials are being considered as a matter of urgency. A second point which also requires resolution before stenched formulations are used more widely is the possibility that the stenching agents might permeate through the Gramoxone packages used by some local repackers, which are believed to be inferior to UK packs (known to retain the stenching agents). If the stenching agent were to permeate through container walls it is believed that this could also lead to consumer resistance.

It is hoped that results of these investigations can be available early in 1977 to enable recommendations to be made on the markets where stenched product will not be introduced.

Evidence on consumer reactions in the UK to pyridine base stenched Gramoxone is being accumulated as a result of the user trial with the emetic formulation (which also assessed reaction to the stench) and from some of the 1976 market research. Results from the user trial indicates some adverse reaction (and the suggestion of some health side effects) to the stenching agent. However the market research seems to show that this has not been translated into unwillingness to use Gramoxone. These findings have not yet been fully analysed and any judgement on their implications must await such analysis.

GENERAL REGISTRATION STRATEGY FOR THE EMETIC FORMULATION

To expedite registration of the new formulations it is hoped that registration authorities can be persuaded that addition of PP796 to paraquat products is a minor formulation change. At the same time we also hope to convince them that the new formulation is a major advance in our attempts to overcome the paraquat poisoning problem, because it effectively reduces paraquat's toxicity. We believe that we shall very shortly have a package of information which should amply satisfy most authorities on both these counts. We hope that as a result of the registration of the new formulation less safe formulations of paraquat will no longer be permitted.

The approach to registration authorities will therefore need to be made with these points in mind. In general the initial approach will be an informal one by our agents to acquaint the authorities with the background to the development, stressing in particular the unique nature of the formulation and the low level of addition of PP796, from which the general inference can be drawn that there are on theoretical grounds unlikely to be any hazards arising from the use of the new formulation. Wherever possible these initial approaches by agents should also involve a visit by a CTL toxicologist to explain the toxicological background to the development. Submission of our full dossier of information on efficacy, toxicology and environmental studies would follow shortly afterwards.

Such a process will, it is believed, obviate the need for us to submit toxicological and environmental information on the compound and the formulations as if PP796 were a pesticide, with the additional work that would be involved. However, we cannot exclude the possibility that some authorities will require additional pieces of information not provided in our initial package.

As a preliminary to the approaches to registration authorities, overseas companies who have not been told in detail about the development of a safer formulation should now be fully briefed about it. A suitable document has been prepared for this purpose.

PROPOSED TIMETABLE FOR INTRODUCTION OF THE EMETIC FORMULATION

Pharmaceuticals Division's production plan for PP796 will allow emetic formulations of paraquat to be introduced into all countries by about mid 1978. However, in some countries (notably the USA) it is possible that registration procedures will delay the introduction until early 1979 or later.

It is proposed that the new formulations should be marketed in some countries in 1977 if registration procedures permit. These countries are:

UK, most countries in Western Europe, Australia, New Zealand, Western Samoa, Malaysia, Japan and possibly Brazil, Indonesia and South Africa.

The case for introduction on an area basis follows.

UK

There is clearly a strong case for early introduction of the new formulation in the UK. The paraquat poisoning problem has been under more severe scrutiny in the UK than in any other country and the registration authorities expect us to be doing more to overcome the problem. Because of the attention given to it in the past and our close relationship with medical people concerned with paraquat toxicity we could expect fairly rapid feedback as to the efficacy of the emetic formulation.

As part of the development programme with the new formulation the UK authorities were informed about its nature in July to enable us to obtain clearance to carry out a series of field trials with co-operating farmers. The present timetable shows submission of information to the authorities to enable sales to begin early in 1977. Early registration in the UK could be a useful tool to use to persuade some other authorities to permit registration.

Western Europe

The toxicity of paraquat has also been of concern in many countries of Western Europe and any introduction of a safer formulation in the UK must be closely followed by its introduction into the rest of Western Europe. Stenched product is already being marketed in some European countries (Eire, Germany, France and Finland) and it is planned to introduce it elsewhere in the Region in 1976-1977.

At a meeting with representatives from the overseas companies in Eire, France, Germany, Belgium, Holland, Denmark, Italy and Spain on 12 October, it was agreed that everything possible should be done to introduce a stenched emetic formulation in Europe in 1977. It is believed that in most cases (an exception could be Italy because of delay in obtaining registration), sales could begin in the last quarter of 1977.

In Belgium it may be necessary to introduce the new formulation in May 1977 as a possible means of overcoming the official requirement for a stenched coloured product to be introduced.

It is proposed that a summary of available data should be sent to the overseas companies to support an informal approach to registration authorities within the next month or so. This should be followed by a more formal submission shortly afterwards. It is hoped that a representative from CTL and PPD will attend early discussions with the authorities since it will be important that the novel aspects of the formulation and the lack of hazards from it are fully understood by the authorities.

North America

Chevron, ICI US and PPD agree that the new formulation should be introduced into the USA as soon as possible. The best strategy is considered to be to get PP796 (at the level of inclusion in 20% paraquat of 0.05%) classified as in "inert" (which is defined by the EPA as a non-pesticidal substance). Chevron are at present reviewing the available information on the compound to determine whether sufficient is available for them to submit it later this year for clearance as an inert. Chevron's recently reported view is that if such clearance is obtained, efficacy and residue trials will be required and these can be carried out in 1977 and approval of the new formulation could be obtained in early 1978 to enable sales to begin in late 1978. Failure to obtain clearance as an inert may mean that PP796 has to be registered as if it were a pesticidal ingredient with the consequent need for a full programme of long-term toxicity studies which could delay introduction of the new formulation for at least three years.

It is proposed that submission of the formulation to EPA for clearance as an inert should be a process independent of any approach to the EPA relating to the decision currently being considered as to whether paraquat's registration should be presumed against. The original deadline for such a decision was to have been 1 October: no firm information is available as to when the decision will now be made, but it is expected in early 1977. A decision by the EPA committee to put paraquat into the rebuttable presumption category might mean that we should draw the committee's attention to the emetic agent immediately.

It is planned to introduce valeric acid stench product into the USA by early 1978: unless this introduction is delayed, it will not be possible to introduce stench and emetic simultaneously.

In Canada it is considered that an initial approach to the registration authorities must be made soon after any submission to the EPA. Clearance of the formulation could be obtained fairly quickly, but since there is no pressing need for early introduction in Canada, sales should begin in early 1978.

No decision has yet been made about introduction of stench in Canada.

Australasia

In New Zealand and Australia there has been increasing concern about paraquat toxicity and we are required to introduce a pyridine base stench product in New Zealand by June 1977. The decision has also been taken to introduce stench product in Australia in 1977.

The fact that there is increased pressure on paraquat in these countries means that they should both be candidates for early marketing of the emetic formulation. In addition there are good contacts between the registration authorities in UK, New Zealand and Australia so that introduction of the emetic formulation in the UK would quickly be known in New Zealand and Australia. There is therefore a strong case for introducing stenching and emetic simultaneously. Registration of the emetic is not thought likely to be time-consuming, so that a late 1977 launch could be possible, causing perhaps a few months' delay in incorporation of the stenching agent.

It has been suggested that Western Samoa would be a good place for a very early launch of the emetic formulation. Suicides using Gramoxone there have increased markedly recently and the medical authorities are concerned about the problem. Dr Glass, the ICI New Zealand medical adviser believes that it would be possible to obtain information about the efficacy of the emetic very quickly; it should be possible to reclaim at least some of the existing Gramoxone in the market to allow a swifter response to the new formulation. It is therefore proposed that the pyridine base stench emetic formulation is launched in Western Samoa early in 1977 (January if possible).

Central America

Registration of an emetic formulation should be straightforward with a minimum of formality, although we shall wish to draw the attention of the authorities to its unique nature. Introduction is not believed to be a matter of urgency so that although registration authorities should be approached early in 1977 with information about the formulation and notice of our intent to register it, marketing should be delayed until 1978.

South America

It is believed that the package of registration information being prepared for the authorities in the UK should also satisfy those in South America. Following briefing of the overseas companies there should be an approach to registration authorities within the next few months. In general, marketing should begin early in 1978. An exception to this is Brazil, where 1977 marketing is more appropriate.

Far East

In Japan there is increasing pressure on paraquat because of large numbers of suicides with the product. Nichino, one of our agents in Japan, have recently been asked by a toxicologist on the registration committee to investigate the possibility of introducing a solid formulation to minimise the risks from paraquat. It is believed that registration of such a "safer" formulation would exclude the use of other "unsafe" formulations of paraquat. Since the emetic formulation is potentially a much more positive contribution to safety than a solid formulation, its introduction in Japan must have high priority. Informal approaches to the registration authorities are proposed within the next 1-2 months with a view to early marketing, although this is felt to be unlikely to be permitted before 1978.

In other countries of the Far East, introduction has lower priority: discussions with authorities should take place early in 1977, in the hope that marketing can begin in 1978. (In some countries efficacy trials may be requested).

Pacific

In Malaysia, we are required to introduce a pyridine base stented formulation by March 1977 because of concern about paraquat toxicity. It is proposed that the emetic should be introduced at the same time as the stent (possibly leading to a slight delay in introduction of the latter). Registration procedures are negligible at present.

Recently pressure on paraquat appears to have increased in Indonesia and there may be a case for introduction of stented emetic product in late 1977. Registration would be assisted by the knowledge that the product was registered in the UK or any other sophisticated market.

In the Philippines registration is straightforward, and should take place during 1977 to enable marketing to begin early in 1978.

The other countries of the area should also commence marketing the emetic formulation in 1978.

Africa

The emetic formulation will be introduced into Africa in 1978. The only exception to this could be South Africa where it may be possible and desirable to introduce it in late 1977.

E Europe

Discussions with registration authorities should begin early in 1977 (shortly after the approaches to Western European authorities). It is believed that registration should take about 1 year and the emetic formulation will therefore be marketed in 1978.

Mediterranean

There is no pressing need for introduction of the new formulation in 1977. An approach should be made to authorities in some of the Mediterranean countries (Israel, Greece and Yugoslavia) early in 1977 with a view to marketing in 1978. In many of the countries (Greece, Egypt, Algeria and Morocco) registration should be straightforward, taking only a few months to complete.

Mixtures

It can be expected that in most countries in which paraquat mixtures with residuals are sold, we shall be required by registration authorities to include PP796 in these formulations also. The technical work with mixtures (stability and emetic efficacy) is not yet complete, but it is considered unlikely that any difficulties will arise. It is therefore proposed that PP796 should be incorporated into paraquat mixtures at the same time as introduction of emetic Gramoxone or as soon as possible afterwards.

Weedol and Pathclear

Significant numbers of paraquat poisoning cases occur with Weedol and in the UK annual deaths from suicide using the product are now at a fairly high level (7 in 1975, 3 in 1976 so far). It is therefore important to incorporate PP796 into Weedol and Pathclear as soon after completion of the technical work as possible.

PRODUCTION PLANS AND PRICE

Pharmaceuticals Division have devised a four-stage process for the synthesis of PP796. The first one tonne production batch is expected to be produced by January 1977: process development work has been going on simultaneously with production of the compound. Existing plant will be used to make the compound. Jealott's Hill Chemists have examined the production process and have been unable to suggest improvements to it.

The present plant for production of the compound has a capacity of 12-16 tpa (sufficient for 4800-6400 t of paraquat). This rate of production (1-1.25 t per month) can be achieved at any time in 1977 provided 4 months notice is given. From the end of 1977, the scale of manufacture can be increased to double or treble the initial rate. Supplies of PP796 will therefore be sufficient to meet all PPD's requirements for the addition to paraquat formulations globally.

The price at which Pharmaceuticals Division are to sell the first tonne of PP796 to PPD is £130/kg which will add 6.5p to the cost of a litre of Gramoxone (£325/tonne ion). The price of £130/kg includes approximately 30% ROC to Pharmaceuticals Division. The plant used to make the first tonne of product will be used for subsequent production: Pharmaceuticals Division will sanction capital to replace the plant used as its use reduces the flexibility for making sales range drugs.

We are assured by Pharmaceuticals Division that the cost of producing PP796 will be decreased by process improvements to be implemented when full production commences and we shall be discussing this with them when details of the process have been finalised (late November).

Forecast production of Gramoxone for the markets in which it is proposed that the new formulation should be introduced in 1977 is shown in Appendix 2. It is expected that in all these markets pyridine base stencled emetic product will be the one to be introduced. Production of the new formulation will not begin for any particular market until registration has been obtained: the most likely times when production can begin are also shown in Appendix 2.

Sufficient PP796 will be available for these introductions to be made and for stocks of the compound to be built up for 1978 use. If the new formulation is registered in some countries (eg Japan and Italy) more rapidly than expected, sufficient PP796 will be available for early introduction.

Suggested quarterly production of PP796 and emetic Gramoxone in 1977
(assuming introductions made as indicated in Appendix 2):-

| | | | | |
|---|-----|-----|-----|-----|
| End of quarter | 1 | 2 | 3 | 4 |
| Max production of PP796 (t per quarter) | 2 | 3 | 3 | 3 |
| Suggested production (t per quarter) | 1 | 1 | 2 | 2 |
| Sufficient to formulate paraquat (t) | 400 | 400 | 800 | 800 |
| Likely actual production: | | | | |
| (1) Begin for W Europe in October (t) | 145 | 382 | 346 | 691 |
| (2) " " " " July (t) | 145 | 382 | 475 | 691 |

(Elsewhere, as in Appendix 2)

Stock of PP796 at end of year Case (2) 1.75 t

Appendix 2 also shows where it is intended to add PP796 to Gramoxone for the 1977 introductions, although these are preliminary intentions and the details have not been worked out. Where the pyridine bases are to be used as stenching agents addition of PP796 can be made in a solution in the pyridine bases, and it is proposed that initially for France, Australia, New Zealand, Malaysia and Indonesia pyridine base plus PP796 is added locally. The alternative, supplying of concentrate containing PP796 (for all except France) would cause some difficulties at Mond: it is not in fact a feasible alternative for Malaysia who will be receiving some concentrate from TAL in 1977. However once all markets receiving concentrate have switched to the emetic formulation it could be preferable to add PP796 to concentrate at Mond, although the implications of this on the customs duty paid on concentrate in some countries have still to be fully assessed. The question of local addition of PP796 to paraquat formulation also needs further consideration because of its possible value as a means of ensuring patent cover is obtained as a result of working the invention.

The cost of PP796 to PPD should be handed on to the overseas companies, although the effect on paraquat price will be hard to assess at a time when the price may need to be reduced for other reasons. However every effort should be made to prevent mark-ups inflating the cost of paraquat to the farmer as a result of the addition of PP796.

PUBLICITY

So far the development of PP796 has been treated as a Company Secret and, as far as is known, no information has been passed to the outside world, with the exception of a few individuals in registration authorities, who have been given the information in strict confidence.

During the next few months, the possibilities that the information about the project will become known to the public must increase. "Leaks" could occur in several ways.

- a) Co-operators involved in the user trials in the UK may pass on the small amount of information they have received about the new formulation.
- b) Officials in registration authorities may discuss it publicly.
- c) The process workers at Mond, who are to be informed about the nature of the new formulation before production begins early in 1977, and those at Pharmaceuticals Division may discuss it publicly.
- d) Poisons Centres and some members of the medical profession will be told about the new formulation prior to launch because it will modify the symptoms of paraquat poisoning and could affect the approach to treatment.
- e) In general it is believed that no label changes will be needed for the new formulation (with the exception of a clear distinguishing mark on the label for identification purposes), although a few countries (notably France) may require that PP796 is identified on the label.
- f) The patents will be published in Belgium and South Africa in October 1977.

We shall therefore require to prepare ourselves to explain to the public the general nature of the new formulation. Publicity is in many respects desirable. We can justifiably claim to have made an important and novel advance in overcoming paraquat toxicity. We shall be in a position to respond to the adverse publicity which paraquat receives in the press (principally in the UK). However, any publicity about the new formulation carries dangers. First it will alert the competition. Second we may raise over-optimistic hopes that we have overcome the paraquat toxicity problem, and if significant numbers of poisonings occur in the future we may find our publicity rebounding to our discredit. Third we cannot be certain that farmers will not be alarmed at the prospect that the new formulation could lead to vomiting when used normally, in spite of our evidence that this is not a problem.

Since paraquat poisoning has only attracted press coverage on a significant scale in the UK and Eire, publicity about the new formulation should be limited to the UK and Eire. It is proposed that a carefully worded press brief should be produced during the next month or so. Release of this to the press should coincide with the launch of the new formulation in the UK and Eire (probably April-May). In the meantime it can be used should any premature leaks about the new formulation occur. (A brief document was prepared on this subject in August to deal with any press enquiries should there have been a leak as a result of the UK field trials with the new formulation.)

See CTL/390, 1976

Appendix 1

Summary

From information following clinical trials and data from experimental animals, it is concluded that PP 796 should be added to paraquat formulations at a level of 5 mg in 10 ml (0.05%). It is estimated that ^{the majority} ~~about 70%~~ of those ingesting 10 ml of this formulation will vomit within an hour.

Introduction

The ICI development compound ICI 63197 produced by ICI Pharmaceuticals Division is a phosphodiesterase inhibitor (Farrell, 1970, Vol II) which has been shown to have a potent emetic action (Bayliss, 1973). This compound has been reclassified by ICI Plant Protection Division as PP 796.

When PP 796 is included in a paraquat formulation in amounts that will cause emesis within 1 hour in dogs and monkeys, the toxicity of the formulation to these species is reduced (Rose, 1976). In order to reduce the toxicity of the paraquat formulation to man, therefore, it will be necessary to add sufficient PP 796 to cause emesis, in a volume of paraquat concentrate that would normally be lethal if ingested. A volume of 10 ml of the 20% w/v paraquat concentrate is considered to be the smallest volume containing a possible lethal amount of paraquat to man (Fletcher, 1974). The question that remains to be answered therefore, is what amount of PP 796 should be added to this volume of formulation?

An emetic response in dogs, monkeys and pigs has been obtained with PP 796 over the dose range 0.1-1.0 mg/kg body weight (Table 1). On this basis a dose of 2 mg/kg was chosen as one that would clearly ensure vomiting in dogs and monkeys, and this dose was, therefore, used for studying the effect of emesis on paraquat toxicity in these species (Rose, 1976).

Studies in dogs using intravenous infusion have suggested that the emetic effect may be a response to the rate of increase in plasma concentration of PP 796 rather than due to a critical plasma concentration being reached (Hepworth, 1971). Certainly, the relationship between dose and emetic effect is steep (Table 1).

Clinical studies (Bayliss, 1973) have indicated that man is more sensitive to the emetic effects of PP 796 than the experimental animals studied, emesis being seen with doses in the range 0.03-0.11 mg of PP796/kg body weight (equivalent to total doses in the range 2-8 mg). In the first human study involving 12 healthy volunteers (average body weight 70 kg), 1 was given 0.25 mg, 1 was given 0.5 mg, 2 were given 1.0 mg, 3 were given 2 mg, 2 were given 3 mg, 2 were given 4 mg and one was given 8 mg. Of these, the volunteer given 8 mg vomited as did one of those given 4 mg. Nausea was a marked effect reported by almost all of the volunteers. It can be seen that when the blood levels of PP 796 in the 2 volunteers given 4 mg are compared, the one that vomited absorbed the compound more quickly than the other (Table 2). This suggests that, as with dogs, the rate of absorption might be critical in determining whether vomiting will occur. After this first volunteer study, one conclusion reached was that "The agent was poorly tolerated at doses above 1-2 mg. Nausea, vomiting, dizziness, sweating and flushing were complained of". As a consequence of this, all further studies were carried out with a maximum dose of 2mg. Of those who took 2 mg, approximately 10% vomited and 60% complained of nausea.

From the limited data available in man, therefore, it can be argued that a dose of 5 mg should certainly cause nausea and ought to induce vomiting in ~~approximately 70%~~ ^{the majority} of those ingesting it (Table 1). It should be noted that the clinical studies were carried out using PP 796 in tablet form. This will have led to an inevitable delay in absorption (Farrell, 1970, Vol I). When present in paraquat formulations PP 796 will be in solution and thus much more readily absorbed. An additional factor that should also be considered is the irritancy of the paraquat concentrate, which causes nausea and vomiting (albeit after a delay of many hours).

In conclusion, the addition of PP 796 to formulated paraquat at the rate of 0.05% (5 mg emetic to 10 ml formulation) should be sufficient to ensure that most people ingesting 10 ml will vomit. Inspection of the statistics of paraquat poisoning incidents reported to ICI shows that most cases involve ingestion of quantities in excess of 20 ml, many suicides involving 50 ml or more. Under these circumstances, and considering 1) the irritant nature of the formulation, and 2) the fact that PP 796 will be in a soluble, dispersed form, it seems highly likely that vomiting will occur within an hour, with a consequent reduction in the amount of paraquat available for absorption.

MSR:SDL

18 Oct '76

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)

TABLE 2

⁺Comparison of blood values of PP 796 in 2 volunteers
given 4 mgs in tablet form

| micrograms PP 796/ml | | | |
|----------------------|-------|-------|-------|
| Hours after dosing | 1 | 2 | 3 |
| Volunteer No 10* | 0.081 | 0.041 | 0.034 |
| Volunteer No 11 | 0.045 | 0.056 | 0.044 |

• Vomited after 30 minutes

⁺ Data from Bayliss (1973)

References

- Bayliss, P. F. C. (1973) A summary of clinical results of the phosphodiesterase inhibitor ICI 63197 in a variety of disease states.
Report No: PH20992B
- Broome, A. W. (1972) Acceptability and emetic activity (of 63,197) in the diet of fattening pigs.
Report No: CPRA14/16
- Davies, G. E. & Hepworth, W (1969) Emetic effects (of 63,197) in monkeys and marmosets.
Report No: CPR095/14
- Farrell, F. G. (1970) ICI 63,197 Submission of evidence to the Committee on Safety of Drugs (Vol. I Chemistry and Pharmacy; Vol. II Pharmacology and Biochemistry; Vol. III Toxicity and Proposed Clinical Trials).
Report No: PH18987C
- Fletcher, K. (1974) in Forensic Toxicology, ed. by B. Ballantyne, published by John Wright and Sons Ltd., Bristol.
- Hepworth, W. (1971) Infusion studies on emetic effects (of 63,197).
Report No: CPR095/20 168A
- Rose, M. S. (1976) The effect of administration of an emetic (PP 796) on paraquat toxicity in dog and monkey.
Report NO: CTL/R/391 (in preparation)
-

PROPOSED PRODUCTION 1977

| Country | Production to begin* | Tonnes paraquat by end of year* | Where added |
|------------------|--------------------------|---------------------------------|------------------|
| UK | March 77 | 688 | UK |
| Belgium | October 77 (April 77) | 6 (12) | UK |
| Denmark | October 77 (July 77) | 3 (3) | UK |
| Eire | March 77 | 65 | UK |
| France | October 77 (July 77) | 97 (139) | France |
| Germany | October 77 (July 77) | 11 (11) | UK (inc. stench) |
| Holland | October 77 (July 77) | 12 (21) | UK |
| Italy | October 77 ⁺ | 46 | Italy |
| Spain | October 77 (July 77) | 9 (38) | UK |
| Rest of W Europe | October 77 (July 77) | 20 (35) | UK |
| Australia | October 77 | 18 | Australia |
| Indonesia | October 77 (July 77) | 34 (68) | Indonesia |
| New Zealand | October 77 | 35 | New Zealand |
| Malaysia | April 77 | 520 | Malaysia |
| Totals | | 1564 (1699) | |

⁺ If registration is obtained

* Dates and production in parentheses assume registration is obtained by May-June 1977 (March in the case of Belgium)

GJAURE: P796

Journal.

PP796 data 1

man (bayliss)

| x | y | |
|-------|-------|---------------------|
| 0.015 | 17 | 17 |
| 0.015 | 18 | 18 |
| 0.035 | 34 | 34 |
| 0.035 | 65 ✓ | 65 - man |
| 0.035 | 68 | 68 |
| 0.04 | 44 | 44 |
| 0.04 | 57 | 57 |
| 0.05 | 56 ✓ | 56 |
| 0.05 | 82 | 82 |
| 0.1 | 85 ✓ | 85 |
| 0.028 | 30 | 30 |
| 0.03 | 20 | 20 |
| 0.03 | 20 | 20 |
| 0.03 | 30 | 30 - man |
| 0.03 | 50 | 50 |
| 0.03 | 70 | 70 |
| 0.015 | 42 | 42 |
| 0.05 | 110 ✓ | 110 - Dog (Phaums) |
| 0.025 | 100 ✓ | 100 |
| 0.05 | 140 ✓ | 140 - Dog (Hayliss) |

21

4

2

df

$$\begin{array}{r} 7922 \\ 5388 \\ \hline 2534 \end{array}$$

16

300.

1217

sig

2

6686.7

5388.

16

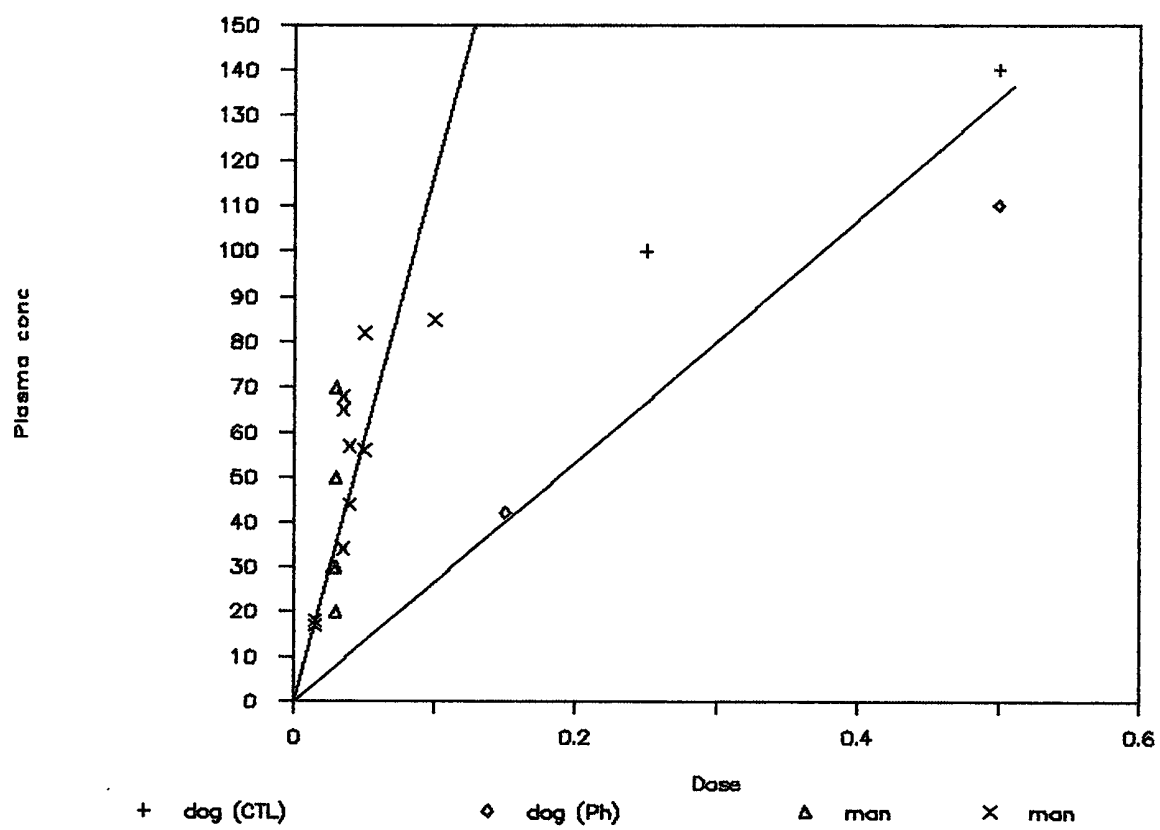
300

NS.

1298.

2

600



Slope of Human data

1172 \pm 110

Slope of Dog data

267 \pm 31

Difference between slopes is statistically significant

References

- * Bayliss, P.F.C. (1973) A summary of clinical results of the phosphodiesterase inhibitor ICI 63197 in a variety of disease states. Report No: PH20992B
- * Case, D.E. and Dunlop, D. (1977) The intravenous administration of ICI 63197 to beagle dogs. Report No: PH23517C
- * Farrell, F.G. (1970) ICI 63197 Submission of evidence to the Committee on Safety of Drugs (Vol. I. Chemistry and Pharmacy; Vol. II. Pharmacology and Biochemistry; Vol. III. Toxicity and Proposed Clinical Trials). Report No: PH18987C *VOL. IV Toxicity Figures*
- RCS *✓* Fletcher, K. (1974) in Forensic Toxicology, ed. by B Ballantyne, published by John Wright and Sons Limited, Bristol
- ✓* Rose, M.S. (1976) The effect of administration of an emetic (PP796) on paraquat toxicity in dog and monkey. Report No: CTL/R/391
- * Todd, A.H. (1977) The emetic effects of ICI 63197 in pigs, monkeys and marmosets. Report No: PH23516C

REPORT REQUEST

From: Reports Centre
Central Toxicology Laboratory
Alderley Park
Nr Macclesfield

To: Reports Centre
ICI Pharms
Mereside

Please supply the following report on loan/~~for retention~~:

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Title & Author(s) .. Todd, A.H. (1977) The ematic effects of ICI 63197 in pigs,
monkeys and marmosets.
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The request is made by Dr G J A Oliver of our
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on Safety of Drugs (Vol. IV. Toxicity Figures)

The request is made by ... Dr G J A Oliver of our

Metabolism & Pharmacokinetics Department and is authorised by

Date requested ... 6 June 1991

Date received

Date returned

| | x | y. | | x | y. | | | | | |
|---|-------|----|---|------------------|-------|-----|----|----|-----|----|
| X | 0.015 | 17 | | 0 | 0.028 | 30 | | | | |
| | 0.015 | 18 | | | 0.03 | 20 | 20 | 30 | 50 | 70 |
| | 0.035 | 34 | | | | | | | | |
| | 0.035 | 65 | | | | | | | | |
| | 0.035 | 68 | Δ | 0.015 | | | | | 42 | |
| | 0.040 | 44 | | 0.025 | | | | | 100 | |
| | 0.040 | 57 | | 0.050 | | | | | 110 | |
| | 0.050 | 56 | | 0.150 | | | | | 400 | |
| | 0.050 | 82 | ▲ | 0.025 | | 100 | | | | |
| | 0.10 | 85 | | 0.050 | | 140 | | | | |

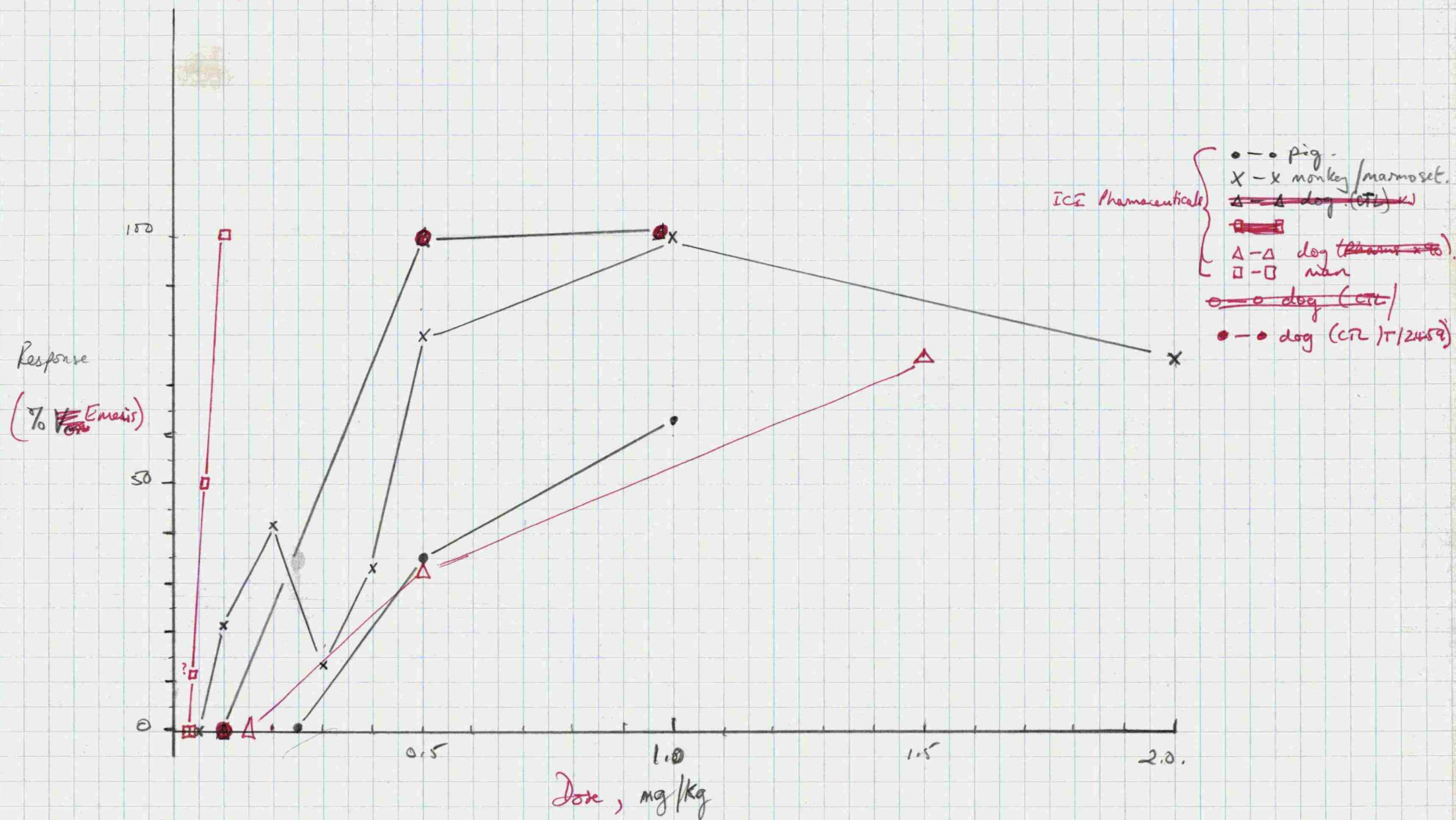
Graph 2.

| Pig x | y. | Monkey. | | Dog. | |
|-------|----|---------|-----|-------|-----|
| 0.25 | 0 | 0.05 | 0 | 0.15 | 0 |
| 0.50 | 35 | 0.10 | 22 | 0.5 | 33 |
| 1.00 | 63 | 0.25 | 42 | 1.5 | 75 |
| | | 0.30 | 14 | | |
| | | 0.40 | 33 | Man. | |
| | | 0.50 | 80 | 0.025 | 0 |
| | | 1.00 | 100 | 0.05 | 10 |
| | | 2.00 | 65 | 0.075 | 50 |
| | | | | 0.10 | 100 |

Dog CTL.

| | |
|-----|-----|
| 0.1 | 0 |
| 0.5 | 100 |
| 1.0 | 100 |

Fig. 1 Parent Emesis v. Dose in Several Species.



7.2 Serum concentrations in the dog (Trial TPD/64)

Two male and two female dogs from each of the three dose groups were investigated after 41, 55 and 90 days treatment with I.C.I. 63,197. The doses were given once daily in tablet form.

The results are given in Tables 24 and 25 and the average concentrations are illustrated in Fig. 7.

There was no significant difference in the serum concentrations in males and females, nor was there a difference in the levels observed at 41 - 55 days and 90 days.

There was a linear relationship between dose and peak serum concentration as shown in Fig. 7 (slope: peak concentration of 0.26 $\mu\text{g.}/\text{ml.}$ per 1 $\text{mg.}/\text{kg.}$ dose). The areas under the average serum concentration-time curves (Fig. 7) in the 0-6 hr. period were 0.245, 0.562 and 1.778 $\mu\text{g.hr.}/\text{ml.}$ for the 0.15, 0.5 and 1.5 $\text{mg.}/\text{kg.}$ doses respectively; again there was a linear dose-response relationship (slope: an area of 1.18 $\mu\text{g.hr.}/\text{ml.}$ per 1 $\text{mg.}/\text{kg.}$ dose).

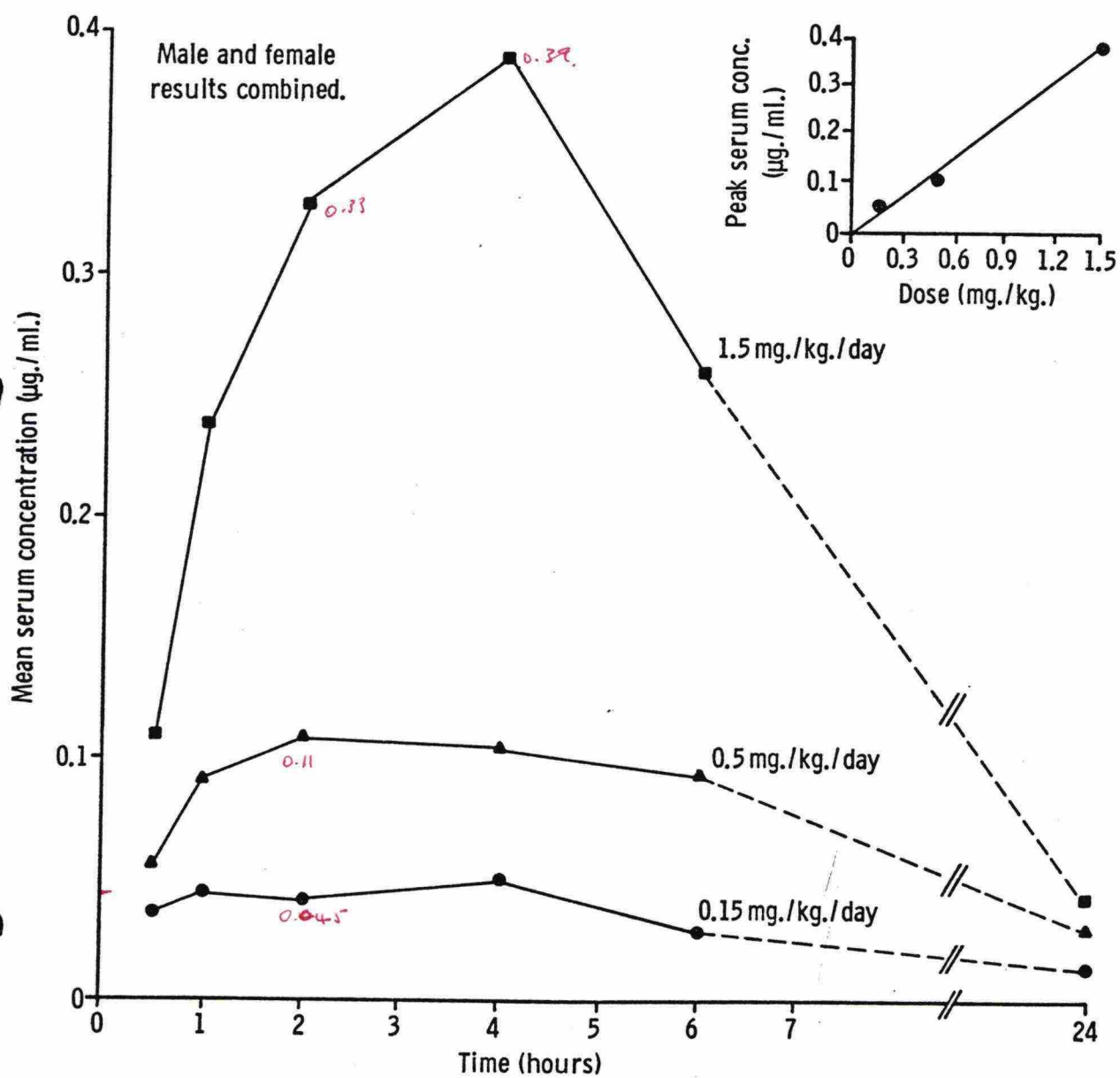
Accurate determination of the biological half-life was not possible from the data obtained, but in 4 cases (Dogs 11637♂, 11650♀, 11657♀ and 11658♀), values of 2.1 hr., 2.6 hr., 2.6 hr. and 5.3 hr. were recorded.

Case + Dose-response study. PH 23517

Figure 7

Average Serum Concentrations After Prolonged Dosing.

I.C.I. 63,197 Dogs (Trial TPD/64)



6.2 DOGS TAD/63

One male and one female dog were dosed with I.C.I. 63,197 daily by mouth as follows:-

| | |
|-------------------|---------------------|
| 0.1 mg/kg - day 1 | 0.9 mg/kg - day 12 |
| 0.2 mg/kg - " 2 | 0.8 mg/kg - " 13-14 |
| 0.3 mg/kg - " 3 | 0.9 mg/kg - " 15 |
| 0.4 mg/kg - " 4 | 1.0 mg/kg - " 16 |
| 0.5 mg/kg - " 5 | 1.1 mg/kg - " 17 |
| 0.4 mg/kg - " 6-7 | 1.2 mg/kg - " 18 |
| 0.5 mg/kg - " 8 | 1.3 mg/kg - " 19-23 |
| 0.6 mg/kg - " 9 | 1.4 mg/kg - " 24 |
| 0.7 mg/kg - " 10 | 1.5 mg/kg - " 25-39 |
| 0.8 mg/kg - " 11 | |

The female vomited approximately 2½ hours after dosing at 0.5 mg/kg 63,197 on the fifth 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 twenty-ninth day.

No histological changes were observed in either of the animals.

7.3 DOGS TPD/647.31 Introduction

Thirty-two beagles were randomly divided into groups of four males and four females and maintained throughout the test on the usual stock diet. Each group was dosed orally with capsules as follows:-

Group 1 - controls, received placebo only, daily for three months.

Group 2 - received 0.15 mg/kg I.C.I. 63,197 daily for three months.

Group 3 - received 0.5 mg/kg I.C.I. 63,197 daily for three months.

Group 4 - received 1.5 mg/kg I.C.I. 63,197 daily for three months.

One male and one female from Group 4 remained undosed for six weeks after the dosing period to assess the reversibility of any lesions.

7.32 General Condition of the animals

One control female developed eczema on its back and was dosed for five days with 2 ml. Streptopen and 1 ml. Betsolan.

After the fifth week of treatment many of the dogs receiving the highest dose salivated profusely before dosing on several occasions. Also one male in the same group refused to eat on days 9 and 10 of treatment.

6/8
3/8
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. It usually occurred after dosing but occasionally the dogs vomited before dosing. Q11659 in Group 4 was sick on several occasions and passed blood in the faeces on day 95: she was killed on that day and found to have an ileo-caecal intussusception.

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

M S Rose

October, 1976

Amended Feb 77

SUMMARY

From the limited evidence of clinical trials and data from experimental animals, it is concluded that PP 796 should be added to paraquat formulations at a level of 5 mg in 10 ml (0.05%). It is estimated that the majority of those ingesting 10 ml of this formulation will vomit within an hour.

The ICI development compound ICI 63197 produced by ICI Pharmaceuticals Division is a phosphodiesterase inhibitor (Farrell, 1970, Vol II) which has been shown to have a potent emetic action (Bayliss, 1973). This compound has been reclassified by ICI Plant Protection Division as PP 796.

When PP 796 is included in a paraquat formulation in amounts that will cause emesis within 1 hour in dogs and monkeys, the toxicity of the formulation to these species is reduced (Rose, 1976). In order to reduce the toxicity of the paraquat formulation to man, therefore, it will be necessary to add sufficient PP 796 to cause emesis ^{within 1 hour} in a volume of paraquat concentrate that would normally be lethal if ingested. A volume of 10 ml of the 20% w/v paraquat concentrate is considered to be the smallest amount containing a possible lethal amount of paraquat to man (Fletcher, 1974). The question that remains to be answered therefore, is what amount of PP 796 should be added to this volume of formulation?

An emetic response in dogs, monkeys and pigs has been obtained with PP 796 over the dose range 0.1-1.0 mg/kg body weight (Table 1). On this basis a dose of 2 mg/kg was chosen as one that would clearly ensure vomiting in dogs and monkeys, and this dose was, therefore, used for studying the effect of emesis on paraquat toxicity in these species (Rose, 1976).

Clinical studies (Bayliss, 1973) have indicated that man is more sensitive to the emetic effects of PP 796 than the experimental animals studied, emesis being seen with doses in the range 0.03-0.11 mg of PP 796/kg body weight (equivalent to total doses in the range 2-8 mg). In the first human study involving 12 healthy volunteers (average body weight 70 kg), 1 was given 0.25 mg, 1 was given 0.5 mg, 2 were given 1.0 mg, 3 were given 2 mg, 2 were given 3 mg, 2 were given 4 mg and 1 was given 8 mg. Of these, the volunteer given 8 mg vomited as did one of those given 4 mg. Nausea was a marked effect reported by almost all of the volunteers. It can be seen that when the blood levels of PP 796 in the 2 volunteers given 4 mg are compared, the one that vomited absorbed the compound more quickly than the other (Table 2). This suggests that, as with dogs, the rate of absorption might be

critical in determining whether vomiting will occur. After this first volunteer study, one conclusion reached was that "The agent was poorly tolerated at doses above 1-2 mg. Nausea, vomiting, dizziness, sweating and flushing were complained of". As a consequence of this, all further studies were carried out with a maximum dose of 2 mg. Of those who took 2 mg, approximately 10% vomited and 60% complained of nausea.

how many studies were there altogether?

Is this evidence of start of DRC

From the limited data available in man, therefore, it can be argued that a dose of 5 mg should certainly cause nausea and ought to induce vomiting in the majority of those ingesting it (Table 1). It should be noted that the clinical studies were carried out using PP 796 in tablet form. This will have led to an inevitable delay in absorption (Farrell, 1970, Vol I). When present in paraquat formulations PP 796 will be in solution and may, therefore, be more readily absorbed. An additional factor that should also be considered is the irritancy of the paraquat concentrate, which causes nausea and vomiting (albeit after a delay of many hours). *significance of this to PP796/safety timescale*
Is time to onset of Xi same as that of vomiting?

In conclusion, the addition of PP 796 to formulated paraquat at the rate of 0.05% (5 mg emetic to 10 ml formulation) should be sufficient to ensure that most people ingesting 10 ml will vomit. Inspection of the statistics of paraquat poisoning incidents reported to ICI shows *x2.0* that most cases involve ingestion of quantities in excess of 20 ml, *x5.0* many suicides involving 50 ml or more. Under these circumstances, and considering (1) the irritant nature of the formulation, and (2) the fact that PP 796 will be in a soluble, dispersed form, it seems highly likely that vomiting will occur within an hour, with a consequent reduction in the amount of paraquat available for absorption.

how quickly evidence for

MSR/JFH/10 Feb 77

Also see

TABLE 2

⁺Comparison of blood concentrations of PP 796
in 2 volunteers given 4 mgs in tablet form

| micrograms PP 796/ml | | | |
|----------------------|-------|-------|-------|
| Hours after dosing | 1 | 2 | 3 |
| Volunteer No 10* | 0.081 | 0.041 | 0.034 |
| Volunteer No 11 | 0.045 | 0.056 | 0.044 |

* Vomited after 30 minutes

+ Data from Bayliss (1973)

References

- ✓ ~~*~~ Bayliss, P.F.C. (1973) A summary of clinical results of the phosphodiesterase inhibitor ICI 63197 in a variety of disease states. Report No: PH20992B
- ✓ ~~*~~ Case, D.E. and Dunlop, D. (1977) The intravenous administration of ICI 63197 to beagle dogs. Report No: PH23517C
- ✓ ~~*~~ Farrell, F.G. (1970) ICI 63197 Submission of evidence to the Committee on Safety of Drugs (Vol. I. Chemistry and Pharmacy; Vol. II. Pharmacology and Biochemistry; Vol. III. Toxicity and Proposed Clinical Trials). Report No: PH18987C
- RCS* ✓ ~~*~~ Fletcher, K. (1974) in Forensic Toxicology, ed. by B Ballantyne, published by John Wright and Sons Limited, Bristol
- ✓ ~~*~~ Rose, M.S. (1976) The effect of administration of an emetic (PP796) on paraquat toxicity in dog and monkey. Report No: CTL/R/391
- ✓ ~~*~~ Todd, A.H. (1977) The emetic effects of ICI 63197 in pigs, monkeys and marmosets. Report No: PH23516C

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13

EFFECT OF ICI 63,197 UPON THE ENDOCRINE SYSTEM IN NORMAL SUBJECTS

(DR. D. DAVIES, MANCHESTER)

PROTOCOL

Fit, healthy University students who are on no drugs (including the contraceptive "pill") were chosen for this study. They gave informed consent to participation.

Subjects were studied in the fasting state.. Blood samples were taken immediately before and at $\frac{1}{2}$, 1, $1\frac{1}{2}$, 2, 3, 4, 5, and 6 hours after a single oral dose of 2 mg. ICI 63,197. Blood samples were assayed for:-

- a) Growth hormone
- b) Insulin
- c) Cortisol
- d) Thyroxine iodine
- e) Glucose
- f) L.H. and F.S.H.
- g) Blood level of ICI 63,197 (at 0, 1 and 2 hours)

A note was made of any adverse reactions complained of. A cup of coffee was taken by the volunteers between $\frac{1}{2}$ and 1 hours, a light meal between $1\frac{1}{2}$ and 2 hours and a cup of tea between 4 and 5 hours.

RESULTSDetails of subjects studied

| No. | Initials | Age (yrs) | Sex | Menstrual cycle | Day of cycle |
|-----|----------|-----------|-----|-----------------|--------------|
| 1 | PWC | 19 | M | | |
| 2 | ID | 23 | M | | |
| 3 | JC | 21 | F | 6/28-35 | 9 |
| 4 | AD | 18 | M | | |
| 5 | JA | 21 | F | 1/28 | 7 |
| 6 | AS | 21 | F | 5/28-30 | 21 |
| 7 | PC-Y | 21 | M | | |
| 8 | MPY | 21 | M | | |

Blood levels of ICI 63,197 ($\mu\text{g/ml}$)

| No. | Time (hrs.) | | | | | |
|-----|---------------|------|----------------|-------|-------|----|
| | $\frac{1}{2}$ | 1 | $1\frac{1}{2}$ | 2 | 4 | 5 |
| 1 | ND | ND | ND | | | |
| 2 | ND | ND | ND | | ND | ND |
| 3 | 0.04 | 0.07 | | 0.05 | 0.03 | |
| 4 | 0.03 | 0.03 | | ND | 0.05 | |
| 5 | 0.03 | 0.03 | | 0.025 | 0.035 | |
| 6 | ND | 0.02 | | 0.03 | ND | |
| 7 | ND | 0.02 | | 0.03 | 0.03 | |
| 8 | 0.02 | 0.03 | | 0.02 | ND | |

ND = not detected, i.e. $0.004 \mu\text{g/ml}$.

Effect on F.S.H. (milli.I.U./ml.).

| No. | Time (hrs.) | | | | | | | | |
|-----|-------------|---------------|----|----------------|----|---|----|----|----|
| | 0 | $\frac{1}{2}$ | 1 | $1\frac{1}{2}$ | 2 | 3 | 4 | 5 | 6 |
| 1 | 1 | 1 | 1 | ND | | | | | |
| 2 | ND | ND | ND | ND | ND | | | ND | |
| 3 | 6 | 5 | 6 | 5 | 5 | 5 | 5 | 5 | |
| 4 | 1 | 1 | 1 | 1 | ND | | ND | ND | ND |
| 5 | 4 | 4 | 3 | 2 | 3 | 3 | 2 | 3 | 3 |
| 6 | 5 | 7 | 5 | 7 | 7 | 6 | 5 | 5 | 5 |
| 7 | 4 | 4 | 7 | 4 | 5 | 4 | 4 | 4 | 5 |
| 8 | 6 | 4 | 6 | 6 | 6 | 0 | 6 | 5 | 8 |

ND = not detected i.e. less than 1 m.I.U./ml.

Possible side effects

These are shown below:-

| No. | Possible side effects |
|-----|---|
| 1 | Nausea and flushing 10 mins. after tablet. Gone by $1\frac{1}{2}$ hours but fainted at 2 hours. |
| 2 | Flushing and slight nausea noted at 10 minutes. |
| 3 | Flushing and slight nausea noted at $1\frac{1}{2}$ - $3\frac{1}{2}$ hours. |
| 4 | Nausea present $\frac{1}{2}$ - 3 hours. |
| 5 | Nausea 30 minutes. Vomited at 45 minutes. |
| 6 | Marked nausea 1 - $1\frac{1}{2}$ hours. |
| 7 | Flushed, sweating and restless at 1 hour. Nausea throughout. |
| 8 | Sweating at 1 hour. |

Extracts from PH 20992C.

Human data from a Volunteer Study with emetic
ed. Baghuis PFC. 1973.

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Pharmaceuticals

TITLE :-

Extracts from reports on ICI 63,197

AUTHOR(S) :-

DATE :-

SYNGERY C REPORT

RESULTSDetails of subjects studied

| No. | Initials | Age (yrs) | Sex | Weight (kg) | Dose ICI 63,197 (mg) | mg/kg. | Vomited |
|-----|----------|-----------|-----|-------------|----------------------|--------|---------|
| 1 | ML | 23 | F | 50.5 | 0.25 | 0.0058 | - |
| 2 | IL | 22 | M | 77.5 | 0.5 | 0.0063 | - |
| 3 | HMCD | 21 | M | 65.5 | 1 | 0.015 | - |
| 4 | PL | 22 | M | 74.0 | 1 | 0.014 | - |
| 5 | MM | 20 | F | 56.5 | 2 | 0.035 | - |
| 6 | IMcL | 24 | F | 56.0 | 2 | 0.036 | - |
| 7 | N | 22 | F | 55.0 | 2 | 0.036 | - |
| 8 | PR | 21 | M | 79.0 | 3 | 0.038 | - |
| 9 | C | 23 | M | 72.0 | 3 | 0.040 | - |
| 10 | APC | 21 | M | 82.5 | 4 | 0.042 | - |
| 11 | CB | 23 | M | 80.0 | 4 | 0.048 | ✓ |
| 12 | CC | 21 | M | 80.0 | 8 | 0.10 | ✓ |

Peter Branley / H/P2
 a. Business guy. / Forthright.

French formulation.
 ratio 12 to 76
 10% in AVO

RESULTSDetails of subjects studied

| No. | Initials | Age (yrs) | Sex | Weight (kg) | Dose ICI 63,197 (mg) | mg/kg. | Vomited |
|-----|----------|--------------|-----|----------------|-------------------------|--------|---------|
| 1 | ML | 23 | F | 50.5 | 0.25 | 0.0058 | - |
| 2 | IL | 22 | M | 77.5 | 0.5 | 0.0063 | - |
| 3 | HMCD | 21 | M | 65.5 | 1 | 0.015 | - |
| 4 | PL | 22 | M | 74.0 | 1 | 0.014 | - |
| 5 | MM | 20 | F | 56.5 | 2 | 0.035 | - |
| 6 | IMcL | 24 | F | 56.0 | 2 | 0.036 | - |
| 7 | N | 22 | F | 55.0 | 2 | 0.036 | - |
| 8 | PR | 21 | M | 79.0 | 3 | 0.038 | - |
| 9 | C | 23 | M | 72.0 | 3 | 0.040 | - |
| 10 | APC | 21 | M | 82.5 | 4 | 0.048 | ✓ |
| 11 | CB | 23 | M | 80.0 | 4 | 0.049 | - |
| 12 | CC | 21 | M | 80.0 | 8 | 0.10 | ✓ |

Blood levels of ICI 63,197These are shown below ($\mu\text{g/ml.}$):-

| No. | Dose of ICI 63,197 (mg) | Time (hrs.) | | | | | | | |
|------|-------------------------------|-------------|-------|-------|-------|-------|-------|-------|-------|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| 1 | 0.25 | 0.016 | 0.006 | 0.004 | 0.005 | | | | ND |
| 2 | 0.5 | 0.008 | 0.017 | 0.005 | 0.005 | | | | ND |
| 3 | 1.0 | 0.005 | 0.019 | 0.004 | 0.006 | | 0.005 | | 0.004 |
| 4 | 1.0 | 0.017 | 0.016 | 0.009 | 0.006 | | 0.008 | | |
| 5 | 2.0 | 0.018 | 0.034 | 0.024 | 0.018 | | 0.007 | | |
| 6 | 2.0 | 0.034 | 0.065 | 0.044 | 0.039 | | 0.015 | | 0.006 |
| 7 | 2.0 | 0.062 | 0.068 | | 0.056 | 0.044 | 0.037 | 0.031 | 0.025 |
| 8 | 3.0 | 0.044 | 0.031 | | | 0.006 | | 0 | 0 |
| 9 | 3.0 | 0.050 | 0.056 | | 0.044 | 0.031 | | 0.018 | 0.025 |
| ✓ 10 | 4.0 | 0.081 | 0.041 | 0.034 | 0.060 | | 0.01 | | 0.014 |
| 11 | 4.0 | 0.045 | 0.056 | 0.044 | 0.033 | | 0.016 | | 0.009 |
| ✓ 12 | 8.0 | 0.047 | 0.085 | 0.068 | 0.041 | | 0.029 | | 0.042 |

ND = not detected, i.e. $< 0.004 \mu\text{g/ml.}$ The half life varies from $1\frac{1}{2}$ - $3\frac{1}{2}$ hours in this series.

✓ - omitted but shown?

10 - 30 mins !
12 - 2 hours !

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 $\frac{3}{4}$ - 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 $\frac{1}{2}$ - 2 hours. |
| 12 | 8.0 | At 30 minutes sweaty, flushed and light headed. Vomited at 2 hours. |

V 0.5

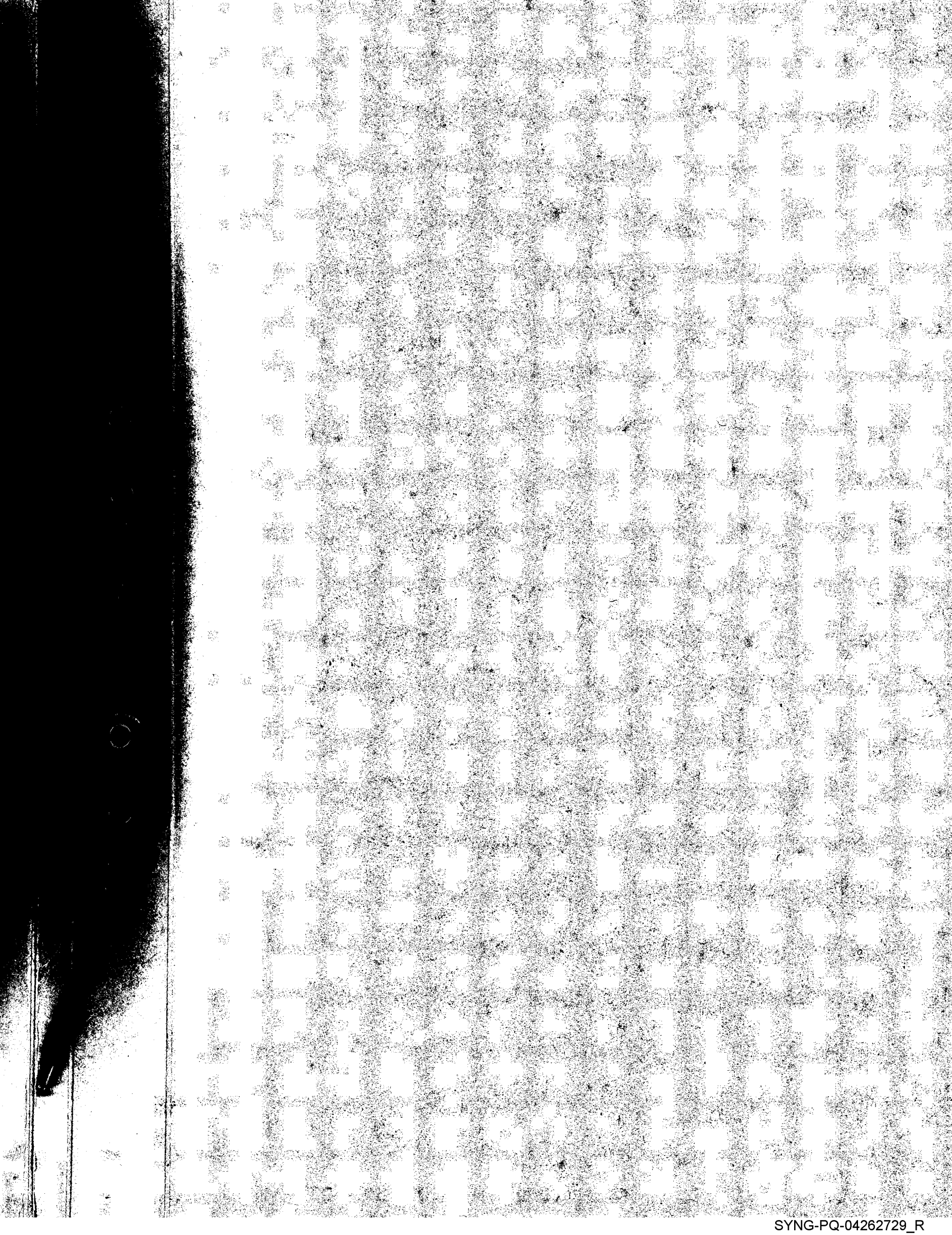
V 2

coincident with peak blood levels.

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.



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