part 1
28

PARAQUAT STRATEGIC ACTION COMMITTEE

MINUTES OF THE SIXTH MEETING OF THE ABSORPTION OF PARAQUAT - SAFER FORMULATION WORKGROUP HELD ON 28 JANUARY 1988 AT JEALOTTS HILL

11 FEB 1988

Those present: W D McClellan - Chairman

T F Tadros		J R Heylings	CTL
C Sales			
M R Parham		C A Spinks	
S Hayes	Jealott's	S J McClellan	Fernhurst
J Burns	Hill	B Domayne-Hayman	
M Moore			
B Young		C Finch	Goldsboro

1. INTRODUCTION (WDM)

Six meetings of the Workgroup have been planned for 1988. The majority will be held at Jealott's Hill and will discuss progress in the Multiple Emulsion Programme. One or two meetings will be held at CTL where the research programmes involved in Gastrointestinal Absorption of Paraquat and Herbicidal Chemistry will be discussed. The relevant people will be informed of the dates of the CTL meetings in due course.

It was agreed to continue the smaller technical meetings at Jealott's Hill, to plan, co-ordinate and report work on a shorter term.

2. FORMULATION UPDATE (CS/TFT)

During December, five replicates of the multiple emulsion formulation 5% B246, Diesel, 1% NPE 1800 (Code 26/08-12) were studied to determine if there were any differences between the formulations over a period of several weeks after preparation.

Dialysis

Paraquat leakage from the five replicate formulations was low (0.2-1.2%). No significant differences were observed between the samples and they generally stabilized with time. A comparison between one day old samples of Diesel and Isopar formulations showed that PQ leakage is lower with Diesel formulations. An NPE B system gave an intermediate result. This is in general agreement with the toxicological data generated in 1987.

Diesel oil

Questions were raised last year about the batches of diesel oil used, the suppliers, and the possible effects of additives on the behaviour of the multiple emulsions. Old and new batches of Exxon diesel were studied along with Phillips diesel with and without additives. NMR studies have shown no differences between samples. Mass specroscopy and surface tension studies are also being done.

Rheology

Differences in viscosity between replicate samples has been observed in the past. Smaller droplets in the emulsion tend to increase the viscosity and this may be related to the ultimate dispersability. Quantification of viscosity will be investigated.

Process

The mixing of the emulsion was described. The primary emulsion can be produced in a few minutes then any extra energy is dissipated as heat. Generally, increasing the speed of mix increases viscosity. Recent studies have however demonstrated that the system is quite robust. The secondary emulsification process is more difficult to control and would be improved by reducing the number of satellite droplents. A collaboration with John Middleton (Runcorn) and the use of static mixers to give uniform droplet sizes is being undertaken.

Gels

The use of gels in the multiple emulsion formulation is being examined. This will provide a physical barrier to reduce PQ diffusion and may improve the toxicology of Isopar systems. Polymethacrylic acid and cross-linking agents may be useful. Gels can be used both in the external phase as well as the internal phase. Furthermore, certain agents will gel effectively at low pH (as exists in the stomach). In this context, improved safening of the product may come from this type of approach.

ACTION: Charles Finch to report back to TFT on any areas of methodology which may help the emulsion programme. In particular physico-chemcial parameters which may be crucial in the formulation process.

3. TOXICOLOGY UPDATE (JRH)

The new members of the group were briefed on the progress to date for identifying a safer paraquat formulation. With the exception of one batch of formulation 26 (5% B246, Diesel, 1% NPE 1800), where paraquat leakage was higher than normal, this multiple emulsion has proved the least toxic during the first year of the programme. The safening factor is probably around 6-fold on a dose basis in dogs compared with GRAMOXONE.

Some debate has arisen as to the usefulness of the rat as a primary screen (prior to dog studies), therefore the power of this test has been examined in a controlled study which has just been completed.

Rat studies

The purpose of the rat study in the past has been to screen out any paraquat formulations which would be likely to be toxic to dogs. A single dose level found previously to be non-toxic with our good emulsions was chosen for this purpose. There is full agreement that survival rate at a single dose level will in no way detect small differences between formulations. However, it will give an indication if the emulsion has broken down. In order to detect smaller changes in the formulation, it was appropriate to examine the power of the rat test at multiple doses with internal and external standards.

Using ten animals at six dose levels the LD50 for 5% B246, Diesel, 1% NPE 1800 was approximately 190mg/kg. An emulsion standard with PQ in the external phase and GRAMOXONE UK as a commercial standard gave very similar LD50 values of 90 and 80mg/kg respectively. Interestingly, the LD50 value of 190mg/kg is so close to the screen dose (200mg/kg) that it is not surprising that high variability was found in the five replicates of formulation 26. The data obtained with GRAMOXONE however was very similar to previous studies during 1987 which suggests little change in biological response.

Future

In order to obtain a more accurate picture of the toxicity of each emulsion formulation we plan to screen at three dose levels between a predicted LD10 and LD90. Results will be compared with a contemporary standard by statistical analysis. In addition, we have two dog colonies comprising a total of 18 animals. Control responses with low doses of GRAMOXONE have been established recently in all animals and we are ready to examine the most promising emulsion formulations in the dog as soon as they are selected.

ACTION: JRH to test future emulsion formulations in the rat and dog as appropriate.

4. BIOLOGY UPDATE (JB/MP)

The characteristics of five replicates of formulation 26 (Batches 08-12) were presented. Physical differences between the formulations were observed. Generally, they all caused filter blockage and this deteriorated with time. The herbicidal efficacy generally decreased with time but no direct correlations were observed.

One point raised was the efficacy of the formulation with and without Agral. It is still not known how much Agral is required, and since the ingredients of the formulation have surface active properties themselves it was agreed that an experiment without Agral is needed for comparison.

Certain tests are required to examine the sprayability of the multiple emulsion in more detail. These include analysis following dilution, filter blockage tests and a determination of what actually reaches the leaf surface. It was also suggested that the spray droplets be analyzed. Testing a multiple emulsion with PQ in the external phase should be considered also to examine the influence of the emulsion components on herbicidal efficacy.

ACTION: MP/JB to compare herbicidal efficacy of a selected emulsion with and without Agral and also with PQ in the external phase.

BY/TFT/CS to look at tests of filter blockage.

5. GENERAL DISCUSSION - PROGRAMME OF WORK (ALL)

Two major approaches will be followed in 1988 with the goal of improving dispersibility of the multiple emulsion without hopefully compromising toxicology to unacceptable levels. These will be based on (i) Isopar formulations and (ii) Diesel/Gel formulations. They should have stability, in the first instance, of at least three weeks. Physical tests of the formulations will detect unsuitable systems. Selected formulations will then be sent to CTL for more extensive toxicology following discussion at regular technical meetings. It is hoped that by the autumn of 1988 that we will be in a position to select a formulation for Field Trials.

6. TRC REPORT

The next TRC meeting is to be held during the last week of March. The format of the Workgroup's contributions was suggested to be as follows:

Introduction	- WDM
Formulations	- TFT/CS
Biology	- MRP/JB
Toxicology	- JRH
Economics/ Business Level	- BD-H
Patents	- HS/JD
Development	- CAS

Contributions should outline the progress made to date in the multiple emulsion programme. A draft report should be sent to WDM by 12/3/88 (for circulation to HS/LLS) and final report by 20/3/88.

DR JON R HEYLINGS
Biochemical Toxicology, CTL

CIRCULATION

W D McClellan)
T F Tadros)
H Swaine)
M Parham)
E J T Chrystal) Jealott's Hill
C Sales)
D Lawrence)
M Moore)
B Young)
J Burns)

C A Spinks)
P J Bramley)
G A Willis)
G Farrell) Fernhurst
P Slade)
S J McClellan)
B Domayne-Hayman)

J R Heylings)
L L Smith)
E A Lock)
I Wyatt)
R C Scott) CTL
M J Farnworth)
R S Morrod)
S E Jaggers)

DRJHMINS
JMPBMISC1

PSAC
PARAQUAT STRATEGIC ACTION COMMITTEE

MINUTES OF THE SEVENTH MEETING OF THE ABSORPTION OF PARAQUAT - SAFER FORMULATION WORKGROUP HELD ON 6 MAY 1988 AT JEALOTT'S HILL

Those present:

J M Fua	- Chairman		
J R Heylings	- CTL		
B Domayne-Hayman	- Fernhurst		
W D McClellan)		M R Parham)	
T F Tadros)		J Burns)	
C Sales)		M Moore)	Jealott's
S Hayes)		B Young)	Hill
J Eshelby)			

1. **MATTERS ARISING**

The improvement of an in vitro system to examine leakage of paraquat from Multiple Emulsion Formulations was discussed. At present, a simple dialysis technique is used to assess PQ leakage. Charles Finch at Goldsboro may be able to improve dialysis testing with a more sophisticated technique. JRH raised the issue of mimicking body temperature in the assessment of PQ leakage which may give more reliable predictions of toxicology. It was also agreed that in vitro systems currently in use at CTL may be useful to study formulations in vitro.

ACTIONS: **CS to run dialysis experiments at 37°C. JRH to send plans of CTL's in vitro systems.**

2. **TRC REPORT - PROGRESS AND ISSUES (WDM)**

The Multiple Emulsion programme to develop a safer paraquat formulation has two major objectives. The first being a 'PREMIER' formulation and the second an 'ACCEPTABLE' formulation as outlined below.

Objectives

(i) Develop a premier formulation which will maintain existing registrations by producing a significant increase in the survival rate from poisoning and which does not incur an unacceptable cost penalty. The target profile for this formulation is:-

a) Toxicity/safety
- 10x reduction in formulation toxicity of Gramoxone
- Inclusion of at least one alerting agent

b) Economic
- Formulation and packing VPC penalty to ICI less than £1000/TE ion.

c) Biological
- Field herbicidal activity >90% 'Gramoxone'
- Tank mix compatability with other herbicides
- Dispersibility acceptable to Field Applicators

(ii) Develop an acceptable formulation to add to the 'Basket Options' ready available.

a) Toxicology
- 5x reduction in formulation toxicity of 'Gramoxone'.

b) Formulation Options
- One which is stable only if wetter necessary to achieve good biological results is added after dilution in the spray tank.

- One which requires a specific chemical stimulus to revive biological activity from a reduced toxicity paraquat formulation. This would require a twin pack on unimix pack.

c) Economic

- Both options would probably have higher costs penalties than the premium formulation profile, but the assessment of its commerical value would have to be assessed on a situation by situation basis.

Business Need - BD-H

(i) 1987 Sales - 15TE £192 million

(ii) Regulatory concerns have led to significant reductions in group profit by reduced sales and/or increased costs.
(Japan, Germany, Switzerland, Egypt, France)

(iii) Currently - reactive strategy (Exec - 1985)
- Alternative formulations ("on the staff; basket")
- None currently available is economically acceptable.

(iv) Multiple Emulsion
- 1° objective: < £1,000/TE ion
- 2° objective: candidate for 'basket of formulations' (twinpack)

Formulation (T F Tadros)

(i) Description of progress from last TRC.

(ii) Future work

a) Improve present formulations based on Isopar M and Diesel oil (objective: 2-3 formulations for field trials by autumn 1988)

b) Continue research improving formulation in (a).

c) Investigate twin-pack concept

d) When field candidate finalised - build in stench, colour and/or emetic.

e) Other effort
WRC - Micro encapsulation
ERC - Model GI tract system (better in vitro)
Univ Strathclyde - Fundamental Research

Toxicology - JH/LLS

(i) Research aspect - understand basic mechanisms of Gastro-intestinal absorption of paraquat in various species.

(ii) Toxicology support for multiple emulsion formulation
- Tested first in rat
- Lead formulations more extensively tested in dogs

(iii) Future work
- Continue research aspects
- Continue toxicology testing of new multiple emulsion formulations with improved dispersibility
- Assess toxicology of alternative formulations that may develop in the study

Biology - M R Parham

(i) Review of studies highlighting poor sprayability

(ii) Developed high throughput herbicide bioassay for new formulations

(iii) Basic activity of Multiple Emulsions (ME)
- ME similar to 'Gramoxone' in glasshouse
- Isopar >diesel
- Small field test agrees with glasshouse

(iv) Sprayability - all tested to date have unacceptable spray characteristics.

Patents - J Downes

(i) Priority specification application was filed 13 January 1987

(ii) Overseas application claiming the formulation process were filed in December 1988.

- European patent application
- National applications

USA	South Africa
Canada	New Zealand
Japan	Hungary
Australia	Israel
etc	

(iii) ICI's freedom to manufacture and sell ME formulations of paraquat.

There is a risk of infringing EXXON's patent 4244816 expiry date 12 January 1988. The risk can not be determined until final formulations are decided upon.

TRC Recommendations - Proposed

(i) That the current level of resources at CTL and in PPD are maintained through 1Q89 to ensure the maximum possible success in achieving the two main objectives for the Multiple Emulsion Formulation.

(ii) That the best candidate formulation(s) available in 4Q88 be taken forwards to a state of "Commercial readiness" as quickly as possible. This formulation would become part of the options available to product management in their defence of paraquat strategy.

(iii) That the resourcing and future of the Multiple Emulsion Research programme be critically reviewed at a TRC in 1Q89.

(iv) That the current level of basic research into the understanding of the absorption of paraquat be continued at CTL through 1Q89. This should also be critically reviewed at the TRC (1Q89).

3. FORMULATION UPDATE (CS,SH,JE,THT)

Three of the objectives for 1988 for the Multiple Emulsion Programme in Formulation Research are (i) Diesel based formulation (ii) Isopar M based formulations and (iii) work of gels.

(i) Diesel Multiple Emulsions (CS)

The objective of Diesel based systems is to produce a sprayable (minimum 3 weeks), stable formulation having a reduced toxicity factor for field testing in August/September 1988.

There are three main areas of optimisation. Firstly, the secondary emulsifier in terms of concentration and ethylene oxide chain length. Secondly, the NaCl concentration is being optimised. Thirdly, the Volume Fraction which was initially $\emptyset_1$ = 0.65, $\emptyset 2$ = 0.38 is also being optimised. Successful formulation is assessed by microscopy, dialysis, dispersion and rheology prior to toxicology and phyto-toxicity testing. It has been found that the relationship between the secondary emulsifier concentration and salt molarity is crucial.

Structuring of the external phase is being actively pursued. Agents such as PVA, Kelzan, Bentopharm, CMC, Guargum etc, are being evaluated. To date the PVA and Kelzan systems show the best dispersibility properties.

Variation of volume fraction can also be crucial. For example, reduction of $\emptyset_2$ (0.5-0.38) gives better dispersibility with NPE 1800. Also variation of the electrolytes in the external phase. Normallly, PQ^{2+} is balanced with Na^+. Studies with other electrolytes such as NH_4Cl, $CaCl_2$, $2H_2O$, $AlCl_3$, $6H_2O$ and $C_5H_5N.HCl$. Al^{3+} and Ca^{2+} give better stabilisation than Na^+ and better dispersibility.

Other ideas tried have been omission of the secondary emulsifier, addition of sucrose, NaCl in the internal phase, inclusion of NPE1800 in the oil phase and replacement of the external aqueous phase by a polar solvent eg. PEG 200.

(ii) Isopar M Multiple Emulsions (SH)

The objective of Isopar M Systems is to retain the good sprayability characteristics but to reduce toxicity of these formulation types. One approach has been to use the non-polar hydrocarbon chain polymer E475 since Isopar M oil is non-polar and better solvation should occur. In order to optimise the system five variables were chosen (i) ratio of primary emulsifiers B246:E475, (ii) NaCl concentration; (iii) NPE 1800 concentration; (iv) Primary volume fraction, and (v) primary emulsifier concentration.

These variables were optimum (as measured by PQ leakage in dialysis experiments) at 9:1 B246:E475, 2M NaCl, 1% NPE 1800, 0.625 ϕ and 10% Primary emulsifier.

Future work with Isopar M systems will involve changing the secondary emulsifier and different physical measurements to assess PQ leakage.

(iii) Gel incorportion into Multiple Emulstions (JE)

Another approach to improve toxicity with dispersible/sprayable Multiple Emulsion formulations of PQ is to incorporate a gel. Gel coating of the droplets will aid dispersion properties and gelling at low pH may reduce bioavailability following oral ingestion.

Polymethacrylic acid (Versicol K11 or K13) obtained from Allied colloids Ltd have surface active properties. Versicol K11 gels at acidic pH in the presence of Al^{3+}. These systems are broken by NaCl but Al^{3+} can be used to structure the gel very well. The gel is likely to be on the surface of the emulsion droplets. This idea will also be used in Diesel based systems to hopefully reduce PQ leakage.

4. OPTIMISATION OF THE ISOPAR M (MM/SH)

A new approach to improving the chances of finding the best combination of variables in the Multiple Emulsion Formulation was presented by Malcolm Moore (Statistics Section). This has been applied to our Isopar M Systems based on dialysis of PQ data, together with a number of component variables. Five of these were chosen and related using contour diagrams:

Variables	Optima
1. Ratio of primary emulsifier B246/E47	9:1
2. NaCl concentration	2M
3. NPE 1800 concentration	1%
4. Primary volume fraction	0.625
5. Total primary emulsifier concentration	10%

The principle of this fractional factorial design is that representative points on a grid can be used to build up a pattern of optimisation. By taking a small number of experimental points the relative importance of each variable can be assessed. This process is repeated until the optimal point is reached. Results suggest that variable 4 (primary volume fraction) is very important. This assumes that low dialysis figures for PQ leakage predict low toxicity in animal studies.

5. TOXICOLOGY UPDATE (JRH)

A total of 15 new Multiple Emulsion Formulations of Paraquat have been tested at CTL in March - April 1988. Unlike last year, more extensive acute toxicity in the rat is carried out prior to dog studies. The Formulations represent a range of new variants which have been shown to be of low PQ leakage in dialysis tests and likely to have better sprayability characteristics than our previous safest Emulsion formulation 26 (B246, diesel, NPE 1800, 2M NaCl). All the formulations contain 100g/l (10%) paraquat ion.

Rat Studies

Although rodent species differ in pharmacokinetic terms to that of dog and man, the more toxic formulations can be filtered out by acute toxicity studies in rats. Our present study design, based on statistical analysis of median lethal dose, compares each formulation at dose levels in a total of 15 animals. The test is standardised with Gramoxone in monthly contemporary studies. Thirteen of the 15 new formulations gave a dose-related effect with median lethal dose ranging from 150-250mg/kg PQ^{++} following a single oral dose. Only 6 of the Multiple Emulsions showed a significant safening worthy of further study in the dog.

Dog Studies

This year, six Multiple Emulsion Formulations of paraquat have been studied in dogs.

Code	Formulation	Dog Studies mg/kg
57/01	B246, Diesel, NPE C, 1.5M NaCl	8, 16
58/01	B246, Diesel, NPE C, 1.5M NaCl, Kelzan	8, 16
60/01	B246, Diesel, NPE C, 1.5M NaCl, Kelzan + PVA	8,
63/01	B246, Diesel, NPE C, 1.5M NaCl	8*,
65/01	B246, Isopar, NPE 1800, 2M NaCl, Versicol	8, 16*,
69/01	B246, Diesel, NPE 1800, $CaCl_2.2H_2O$	8*,

(* in progress)

The above Formulations are primarily all Diesel oil based. Our strategy at CTL is to commence dosing with any new formulation at a known sub-lethal PQ dose (8mg/kg). Thus, if the Emulsion completely breaks down, the animal will be symptom-free but blood profiles will indicate no reduction in Gastrointestinal absorption of paraquat. Such formulations are not re-tested at higher dose levels.

Results to date with 4 Emulsion formulations have been encouraging at 8mg/kg. Two formulations have been advanced to 16mg/kg still without any symptoms of paraquat intoxication. Contemporary controls with Gramoxone in a total of 10 dogs gave very similar results despite one colony being one year older and, importantly, there was no difference in plasma PQ profile when dogs were dosed by capsule or gavage tube. At 8mg/kg the Kelzanformulation (58/01) resulted in lower blood PQ levels compared to its contemporary control (57/01).

At 16mg/kg, these two formulations were non toxic and gave similar PQ levels in 3 dogs each. Addition of polyvinyl alcohol (PVA) to this Emulsion type did not alter plasma PQ profile seen at 8mg/kg with 57/01 or 58/01.

The fourth new Emulsion tested in dogs (65/01) was a new concept. It is based on Isopar M oil and NPE 1800 as secondary emulsifier. Previous Isopar M formulations had good dispersibility characteristics, but were invariably toxic. In addition, polymethacrylic acid (Versicol K11) was used in the formulation. Versicol may coat the droplets and gels at low (gastric) pH. At 8mg/kg this formulation (65/01) gave reduced plasma PQ (both peak and AUC) compared to 8mg/kg PQ as Gramoxone, and was, in fact, the lowest AUC value of all the Emulsions currently under test. A dose level of 16mg/kg is scheduled for the beginning of June.

ACTION: JRH to co-ordinate the toxicological testing of Emulsion Formulations of Paraquat and to establish likely safening factors over Gramoxone in the dog.

6. **BIOLOGY UPDATE** (MP)

Since the last meeting held on January 28 there has been no testing of Multiple Emulsion Formulations for Herbicidal activity.

ACTIONS: MP/JB to test a single Isopar-based Formulation (65) for herbicidal activity in the Glasshouse. BY to check the dispersibility of Formulation 65.

7. **STRATEGY FOR 1988** (All)

It was agreed that further batches of Formulation 65 would be prepared then tested simultaneously at CTL and for Herbicidal activity at Jealott's Hill. Research on diesel/gel based systems and inclusion of emetic in the formulations would be pursued. The extent of Biology testing will depend largely on the success of dispersion and sprayability of new formulations.

8. **ANY OTHER BUSINESS** (All)

The use of a biodegradable shell around PQ was discussed. Such a formulation could be reactivated on the plant leaf by sunlight. It was generally thought that the amount of material needed and manufacturing technology would impose high cost penalties to such an approach.

Use of non-emulsions to safen PQ was also raised. Solid formulations, Dextrans, other sugars etc. may still be feasible but the main stream effort will remain on the Multiple Emulsion Programme.

The issue of patents was discussed with reference to Formulations which gel at low pH. Companies like SDS (Japan) could well be close to our idea.

ACTION: THT to discuss this with John Downes.

DR JON R HEYLINGS
BIOCHEMICAL TOXICOLOGY, CTL

CIRCULATION

J M Fua	
W D McClellan	
T F Tadros	
H Swaine	
M R Parham	
E J T Chrystal	
D K Lawrence	
B Young	
M Moore	ICI Agrochemicals
C Sales	Jealott's Hill
S Hayes	
J Eshelby	
J Burns	
P K Thomas	
J E Downes	
E Paterson	
B Domayne-Hayman	
C A Spinks	
G M Farrell	ICI Agrochemicals
G A Willis	Fernhurst
P J Bramley	
P Slade	
J R Heylings	
L L Smith	
E A Lock	
I Wyatt	
R C Scott	CTL
M J Farnworth	
R S Morrod	
S E Jaggers	

COMPANY SECRET This document has been circulated by

PSAC
PARAQUAT STRATEGIC ACTION COMMITTEE

Paraquat.

17 AUG 1988

MINUTES OF THE EIGHT MEETING OF THE ABSORPTION OF PARAQUAT - SAFER FORMULATION WORKGROUP HELD ON 26TH JULY 1988 AT JEALOTT'S HILL

Those present: J M Fua - Chairman
J R Heylings - CTL
E C Paterson - Fernhurst
C A Spinks - Fernhurst

T F Tadros) M Moore)
C Sales) J Burns) Jealott's Hill
S Hayes) B Young)
P K Thomas)

1. MATTERS ARISING

Dialysis experiments are used to determine the leakage of paraquat from the Multiple Emulsion formulation. Concern had been raised at the last meeting as to the effect body temperature may have on the leakage of the Isopar and Diesel systems when compared with conventional room temperature estimations.

A new method was consequently developed by the Formulation Group to measure dialysis in a water-jacketed chamber connected directly to a spectrophotometer for PQ estimation. Isopar M systems surprisingly showed faster rates of PQ leakage at 20°C compared with 37°C. Diesel systems gave a similar result but this was not as dramatic over the first 2 hours. It

was suggested that the temperature-related release of PQ could be due to different surfactant solubilities and alteration in osmotic balance of the formulation. It will be of interest to examine lower temperatures to see if there is a trend.

ACTION: SH to further investigate the relationship between temperature and leakage over a range of temperatures.

2. TRC - OCTOBER 1988 (JMF)

The TRC meeting has been scheduled for 10/10/88. The proposed areas for the meeting are as follows:-

1) Safer Formulations
2) Gastrointestinal Absorption
3) New Antidotes
4) Alternative Chemistry

These were the original prososals agreed in October 1986. However, the majority of the Workgroups effort since this time has centred on the Multiple Emulsion programme.

Timetable

Final Draft - 6/9/88 (Decide on Presenters)
Steering Group Meeting - 13/9/88
Typing - 26/9/88
Report Issue - 3/10/88

ACTION: Contributors to send Jee Mok final drafts by September 6th.

3. FORMULATION RESEARCH (CS, SH, PT)

(i) Diesel Systems

The Diesel based Multiple Emulsion Formulations of Paraquat are being further developed to improve their dispersion properties in water. Addition of Versicol K11 to the formulation coats the surface of the drops and may be useful to improve the toxicity of the more dispersible Diesel Emulsions. Alteration in volume fraction, electrolyte and secondary emulsifier have been examined. The Calcium based system (69/01) has good dispersibility properties at volume fractions of ϕ_1 0.65 and ϕ_2 0.38. The stability of this formulation is being examined (-5 to 50°C) for larger batches. Preliminary data suggest good stability. Up to three months sprayability tests have also been carried out on these systems. They disperse well but flocculate to some extent. This may not be a problem with certain knapsack spraying where there are no fine filters.

(ii) Isopar M/Versicol Systems

The addition of polymethacrylic acid (Versicol K11) to the Isopar system has been studied. This material, in the presence of a cross-linking agent (eg. Al^{3+}) will produce a gel at low (gastric pH) but remains in solution at neutral (tap water pH). Formulations 64 (no Versicol) and 65 (1.5% Versicol) have been compared. These Multiple Emulsions are stable for 2-3 weeks. Thereafter they become very oily and more difficult to dilute. Other Versicols have interfered with the formation of the Emulsion. However, by varying the secondary emulsifier or the electrocyte used, better overall dispersion/stability properties may be found.

(iii) Variation of the Electrolyte

Use of Ca^{2+} in place of Na^{+} in the external phase has produced interesting results both in the physical properties of the Multiple Emulsion and in

Toxicology (See Section 5). Calcium-balanced systems have improved the dispersion and stability properties of Diesel Emulsions (as described above). The cation balance the PQ^{++} in the internal phase osmotically to prevent disruption of the droplets. However, each cation has different osmolarity versus molarity curves. Thus, at 1.5M, Ca^{2+} has a greater osmotic effect than Na^{+} at the same molar concentration. Other cations never previously tried in a Multiple Emulsion formulation have therefore been examined. These include Ba^{2+}, Mg^{2+}, Al^{3+}, and Fe^{3+} (all as chlorides). Barium systems were poor. The other systems are to be sent for toxicological evaluation. Another possiblity is to use diquat in the external phase. A 1.5M concentration of DQ is insoluble in the external phase but further work is in progress with lower concentrations of diquat.

ACTION: Examples of Emulsions based on different electrolytes to be sent to CTL.

(iv) New Isopar M Systems

The Isopar M Multiple Emulsions generally have better dispersion properties in water compared to Diesel based Emulsions. A variety of new approaches are being examined to optimize this Emulsion type. For instance, the NPE 1800 can be replaced with other secondary emulsfiers eg. synperonics A7-A50, NP8-NP50, Tweens, Pluronics etc. The leakage of such systems is being compared. The process for making the primary and secondary emulsions can be varied. For instance at ϕ_1 = 0.54 large droplets are produced, viscosity is low but there is high leakage of PQ. In the secondary emulsfication the speed and time of mixing can alter the final leakage. It may be useful to centrifuge the formulation and compare the fraction compositions of oil, foam, emulsion and water to predict behaviour of the formulation.

(v) Inclusion of Emetic

Any potential commercial formulation would probably contain the safening agents currently present in Gramoxone. It is useful to know at this early stage whether addition of the emetic (PP796) in any way compromises the

formulation of a Multiple Emulsion and its ensuing toxicology. A 2 gram per litre PP796 formulation has been made using an Isopar M System.

ACTION: The concentration of emetic should be agreed with the Yalding group ie. whether it is relative to the amount of bipyridyl or final volume of concentrate (THT).

(vi) Twin-Pack Emulsions

There are several advantages to the development of a separate pack system. A primary Diesel oil based Emulsion can be made which is stable for a relatively long period of time. It can then be easily mixed with the external phase containing surfactant and remain stable/sprayable for at least 24 hours. The primary is probably our safest formulation tested so far in dogs. On mixing with surfactant, a Multiple Emulsion is formed which previous trials have shown to be significantly better to handle when sprayed within hours of preparation. Addition of alkyl glucoside to the external (separate) phase greatly improves the dispersion properties and this can be optimised with regard to storage stability and ease of dispersion in water. Furthermore, the volume fractions can be altered to optimise the relase of PQ following addition of water.

There was considerable debate as to whether the paraquat-containing part of the separate pack would contain 10 or 20% PQ ion. For instance, if there is a 1:1 dilution of primary emulsion with external phase, the final concentration would be 5% PQ. This would hopefully counteract the loss in safening once mixed.

The issue of cost associated with such a formulation was raised. Separate packs or a vessel which pre-mixed the phases when opened would be associated with a cost penalty. However, if sold separately the PQ-containing part would be the one used as a suicide agent and this would hopefully meet our safening criteria. The major problem appears to be ensuring that the two phases are mixed before any water is put into the spray tank.

4. TOXICOLOGY OF THE MULTIPLE EMULSIONS (JRH)

(i) Isopar M/Versicol System

Formulations 64 (No versicol) and 65 (Versicol) based on Isopar M have been extensively studied in rats. At least three batches of each formulation have been given orally to 5 rats at 150, 175 and 200mg/kg. The overall survival rate was much higher for the Versicol containing formulation (54%) compared with the control Isopar M formulation (29%). The first dog study has recently been completed with Formulation 65. It showed a clear reduction in plasma PQ at 8mg/kg (c.f. Gramoxone). At 16mg/kg it was non-toxic suggesting at least 2 fold safening. In vitro studies at CTL have also demonstrated that formulation 65 disperses well at pH's above 4. At pH3 it begins to coagulate slightly. At pH2, the formulation gels instantaneously on addition to water (1:50) and a large amount of flocculated material is left after shaking. Formulation 64 dispersed very well in water over a pH range 1-7. Interestingly, the prevailing gastric pH in dogs and man is lower than the rat so this effect may well be more successful in higher mammals compared to rats. The mechanism of reduced toxicity will be further evaluted if we can confirm a reduction in plasma PQ levels in the dog with fresh batches of Emulsions 64 and 65 at higher dose levels. Research studies have suggested that the gelled formulation will empty from the stomach at a slower rate thus avoiding high plasma peaks which are a feature of toxic paraquat formulations.

ACTION: Formulations 64 and 65 to be compared directly in the dog (JRH).

(ii) New Diesel based Systems

Since the May 6th meeting, ten new diesel based formulations have been tested in rats at CTL. Most of this group have been relatively more toxic than previous B246/Diesel/NPE 1800 Emulsions. Generally, they offer greater dispersion properties in water but most have had insufficient safening in

rats worthy of submission to dog experiments. A good proportion of these formulations have calcium in place of sodium in the external phase. The least toxic calcium-based formulations 69 and 82 have been looked at in the dog to check examples of this new series in our most predictive model. At 8mg/kg, formulation 69 had a similar plasma profile to the same dose of Gramoxone. Formulation 82 gave a lower plasma PQ AUC at 8mg/kg and will be re-tested at 16mg/kg in August.

ACTION: Formulation 82 to be further evaluated in dogs at higher dose levels (JRH).

(iii) Twin-Pack Systems

Formulation 75, a Primary Emulsion of B246 and Diesel oil gave our best result of 1988 in rat studies. This formulation was also mixed with external phase containing alkyl glucoside and instantly formed the Multiple Emulsion (code 77). This was then dosed to rats within 10 minutes of mixing. Mortality rate was significantly higher on a mg/kg basis at all 3 dose levels than the Primary system alone. The same procedure was carried out in dogs with 75 and 77 at 8mg/kg. As found in rats the Primary Emulsion gave a much lower plasma PQ AUC compared with the freshly prepared Multiple Emulsion. However, both results demonstrated clear safening factors compared with Gramoxone. This relative difference is currently being compared at 16 and 32mg/kg in the dog.

ACTION: Primary Emulsion to proceed at higher dose levels in dog studies with the Multiple Emulsion one dose level behind (JRH).

5. BIOLOGY STUDIES AND FIELD TRIAL CANDIDATES (JB)

Only a limited amount of work has been undertaken by Weed Science since the last meeting. Formulations 64 and 65 (Versicol) have been tested in the 4 species bioassay versus Gramoxone. Data was compared with the old 'bronze' standard B246/Diesel/NPE 1800 system. The large scale batches

(formulations 64/03 and 65/03) were dispersible and were as good as the bronze standard in glasshouse studies. The smaller batches of the same formulation had poorer herbicidal activity and caused filter blockage at the high rate. It is generally felt that a Field Trail will demonstrate more accurately the herbicidal efficacy of our best Multiple Emulsions.

There was considerable debate as to which Emulsions should be submitted for Field Trial testing this Autumn. THT proposed that we include Formulation 82 (The Calcium based Diesel system) in order to test our most dispersible/stable Diesel system. JRH suggested that we should only submit Emulsions with a clearly defined safety factor in the dog. Data would ve available soon as to the safety limits of Formulation 82. It was agreed that the Primary Emulsion (Twin Pack) probably offers the best short-term hope and should be evaluated in the Field. The Versicol systems based on Isopar M are also worthy candidates. By September we will have more dog toxicology and results of spray testing/herbicidal activity on which to base our final judgement.

ACTION: A separate discussion on Field Trial candidates should be arranged (JMF).

6. OTHER PARAQUATS (ALL)

Some new sulphated sugars which may bind bipyridyls effectively have arrived through ICI Japan. A separate meeting (possibly the Steering Group) will discuss what action will be taken with these agents.

ACTION: EP to take this issue to the Steering Group.

7. FUTURE MEETINGS

The next meeting of the Workgroup is scheduled for September 6th 1988.

DR JON R HEYLINGS
BIOCHEMICAL TOXICOLOGY, CTL

CIRCULATION

J M Fua	
W D McClellan	
T F Tadros	
H Swaine	
M R Parham	
E J T Chrystal	ICI Agrochemicals
D K Lawrence	Jealott's Hill
B Young	
M Moore	
C Sales	
S Hayes	
J Burns	
P K Thomas	
J E Downes	
E Paterson	
C A Spinks	
G M Farrell	ICI Agrochemicals
G A Willis	Fernhurst
P J Bramley	
P Slade	
J R Heylings	
L L Smith	
I Wyatt	
R C Scott	CTL
M J Farnworth	
R S Morrod	
S E Jaggers	

JDQBCMISC

PARAQUAT STRATEGIC ACTION COMMITTEE

28 SEP 1988

MINUTES OF THE NINTH MEETING OF THE ABSORPTION OF PARAQUAT - SAFER FORMULATION WORKGROUP HELD ON 6TH SEPTEMBER 1988 AT JEALOTT'S HILL

Those present: J M Fua - Chairman
J R Heylings - CTL

Th F Tadros)
C G Sales)
S E Hayes)
P K Thomas)
J Burns)
B W Young)
A Chapple)
M Moore)
Jealott's Hill

PQ

1. **MATTERS ARISING**

Dialysis experiments to study leakage of MEF's at a variety of temperatures have not yet been done.

ACTION: SH

The concentration of emetic (PP796) in a 100g/l Multiple Emulsion Formulation should be established.

ACTION: ThT

2. **NEW FORMULATIONS (CS, SH, PT)**

(i) Potential Field Trial Candidates

A variety of MEF's have been established as potential Field Trial candidates following extensive toxicology. Prior to selection, Glasshouse studies have been run by weed science in addition to tests of sprayability (see sections 3 and 5). The formulations under consideration are abbreviated to a code as follows:-

Code	Primary	Secondary	Oil	Electrolyte
82	B246	NPE 1800	DIESEL	$CaCl_2$
87	B246	NPE 1800	ISOPAR	NaCl
89	B246	NPE 1800 VERSICOL K11	ISOPAR	NaCl
26 (JF10991)	B246	NPE 1800	DIESEL	NaCl
75	B246	-	DIESEL	-
77	B246	SEPARATE NPE 1800	DIESEL	NaCl
90	B246	NPE 1800	DIESEL	$MgCl_2$

It was decided that 4 formulations (82, 87, 75 and 90) should be tested in the Field to compare with data already generated in the Glasshouse tests. Three rates will be used, the middle rate with and without Agral.

ACTION: Formulation and Weed Science to coordinate arrangements for the Field Trial to take place by the end of September.

(ii) Electrolytes in the external phase of Diesel systems

Since the last meeting more extensive studies have been carried out with calcium and magnesium based MEF's. The Mg versions of B246/Diesel/NPE 1800 have proved much less toxic and the concentration of this electrolyte has been varied to optimize this property. Generally, both Ca and Mg systems give low PQ dialysis values (<7%). Also, they are good dispersers in water. The problem now is to reduce post-dilution flocculation. This may be overcome by incorporating other polymers to the system or mixing NPE 1800 with NPEC. Anionic surfactants or combinations of B246 with Arlacel 83 or Span 80 may also reduce flocculation.

(iii) Isopar M Systems

Since the discovery of the safening properties of Mg in diesel MEF's, this has now been incorporated in Isopar M systems. A variety of $MgCl_2$ molarities and different volume fractions have tried to optimise such a system. For instance, 0.75M $MgCl_2$ gives the lowest dialysis values. The first toxicological results on Isopar-Mg systems are reported in Section 3.

Inclusion of 2g/l emetic (PP796) in Isopar M MEF's has not significantly altered dialysis values. At this stage there have been no compromises in the formulation with emetic included.

The differences in toxicology between Isopar M and Diesel oils remains. The use of other oils eg. Exxsol D80 (<1% aromatic), Escaid 100 (25% aromatic) or mixtures of these oils are being examined to investigate the importance of aromaticity of the oil.

A new method of assessing the MEF's by centrifugation is being explored. For instance, a change in aromatic content of the oil may alter the separation of fragments.

(iv) Primary Emulsions and Twin Packs

The 100g/l Primary Diesel Emulsion has performed well in spray tests herbicidal studies and in toxicology where it is probably at least 6x safer than Gramoxone. However, there are strong commercial drawbacks in the introduction of such a formulation. Firstly, it has to be mixed with external phase prior to water (hence it would probably have to be a twin-pack). Secondly, if the final mixed concentrate has to be 100g/l then the Primary Emulsion part of the pack would have to be 200g/l.

High strength MEF's are more process sensitive. A 200g/l primary can be made, but the secondary process formed on mixing with external phase makes this a difficult approach. Use of ether sulphate instead of alkyl glucoside may improve the process.

ACTION: Formulation to continue work on Diesel and Isopar M systems to hopefully reduce flocculation problems. The amount of effort by the group to produce a high strength Primary Emulsion will be reviewed (ThT).

3. SPRAYABILITY TESTING (AC, BY)

An extensive report on a small number of Multiple Emulsion Formulations has outlined the various criteria which are important in assessing the sprayability of the formulation. These are based on subjective assessments. The move from the Glasshouse to the Field can present its own problems in terms of how the MEF is handled. There was considerable debate around the interpretation of experiments performed on a small scale and how the MEF's are likely to behave under Field conditions. Obviously, the ultimate goal of this programme is to produce a good diluter with no flocculation and no trace of formulation on the filters. The objective of sprayability tests is to see how close we are getting to a sprayability a "practical" MEF.

Compared to formulation research, toxicology and glasshouse studies, there has been very little done on tests of sprayability. What we do know is that the present generations of MEF's dilute much better than previous standards. Assessing the degree of flocculation after dilution is not

easy, but the group agreed that a much more rational approach to such assessments is paramount if the project is to succeed. To make the step from Laboratory to Farmer with a formulation which has the potential of being 10x safer than Gramoxone is not going to be made in a few weeks. Field Trials at least will tell us whether particular MEF's are unlikely to be practical.

The recent sprayability studies attempted to rank 4 formulations from the point of view of Field Trial spraying (82, 87, 89 and 26). The "twin-pack" formulation was also examined. They were ranked from best to worst: 87, 82, 89, 26 (see key on Section 2 for formulation details). With respect to the twin-pack (75), no problems are expected from the point of view of Field trial spraying. The sprayability studies suggest that more recent formulations are better in terms of sprayability, compared with our original standard JF10991 (26). However, these formulations still need to be improved to be acceptable under all conditions. The proposed Field Trial will provide more data on how close we are to achieving a sprayable formulation.

ACTION: A quantitative method for assessing sprayability should be used to more accurately distinguish between different formulations (BY).

4. TOXICOLOGY OF NEW EMULSIONS

Since the 26th July meeting a further 13 new Multiple Emulsions have been tested in rats. Four dog studies have examined the absorption from our least toxic formulations.

(i) Primary Emulsion (75)

This remains our least toxic Emulsion tested to date in both rats and dogs. The latest dog study has confirmed that this formulation has at least a 6x safety factor over aqueous paraquat. Three dogs have received 8, 16, 32 and 48mg/kg with no signs of toxicity and plasma AUC values are all below 25µg/ml/hr (lethal values are above 40µg/ml/hr). This formulation has also been mixed with external phase NPE 1800 to produce the 50 g/l sprayable multiple Emulsion (77). Test so far have shown this product to be safe at 8, 16, and 24mg/kg with AUC values still below 30µg/ml/hr at 24mg/kg. Thus, the pre-mixed twin-pack product has probably an intrinsic 3x safety factor (doubled to 6x since it has been diluted 1:1 already).

(ii) Diesel Based Emulsions (82,90)

Formulation 82 contains calcium in the external phase. Recent dog studies have shown this formulation to be safe at 16mg/kg (AUC = 32). The next dog study at the end of September will test the 4x level (32mg/kg).
Formulation 90 is identical apart from $CaCl_2$ being replaced with $MgCl_2$.

As a new variant this formulation was first tested in rats. To our surprise, formulation 90 was non-toxic at screen dose levels in a total of 15 rats. Dose levels were pushed to 200mg/kg with 1/10 mortality and 2/5 mortalities at 250mg/kg (LD50 for Gramoxone in rats is about 90mg/kg). Further rat studies with $MgCl_2$ or $CaCl_2$ added to aqueous paraquat clearly demonstrated that calcium enhances paraquat toxicity in this species and increased blood levels of the herbicide upto 5 fold. Magnesium added to Gramoxone had no such effects. Our first dog study with Emulsion 90 (Mg) gave our lowest AUC value at 16mg/kg observed since the programme started (13µg/ml/hr). The next study is arranged for October 18th at 32mg/kg.

(iii) Isopar M Based Emulsions (87,89)

Formulation 87 and 89 are based on the more "sprayable' Isopar M system. The only difference between them is that 89 contains the gel Versicol K11. The principle being that at stomach pH the K11 will produce an irreversible gelled formulation but remain a solution in tank mixes. Emulsions 87 and 89 were compared at 16mg/kg in dogs. Neither was toxic at this level but interestingly the plasma profile over 24 hours differed quite markedly. The Versicol Emulsion showed no early high plasma paraquat peaks and spread the response over a longer time period. This response could be beneficial in treating poisoned victims and would make emesis much more effective. The Isopar M system is currently being tested at 24mg/kg. Experiments last year found the Emulsion to be lethal at 32mg/kg.

(iv) Emetic in Isopar M Emulsions

The first study with 2g/l PP796 included in an Isopar M MEF was successful. The emulsion was not compromised at this concentration of PP796 and no differences in toxicology were observed in rats at 3 dose levels in a controlled study.

(v) Electrolytes in Diesel Formulations

Our previous Diesel systems have always contained sodium chloride as an osmotic balance to the paraquat. Following the recent observations with Calcium and Magnesium salts a further 3 cations were examined. Barium chloride did not produce an Emulsion, iron and aluminium chloride did, but they were found to be more toxic to rats in a Diesel Emulsion when compared with standards. A approximate ranking of the toxicity of various ions and their dilutability in water is as follows:-

Safening Mg > Na > Ca > Fe > Al

Dilution Ca = Mg > Na

Magnesium and Calcium systems are osmotically the same, but from rat studies magnesium offers a better safety factor.

Further studies are in progress which are examining the optimal molarity of $MgCl_2$ in Diesel systems. Furthermore, $MgCl_2$ has now been incorporated into Isopar M systems. Research studies are also in progress to examined the role of calcium and magnesium in the absorption of paraquat from the Gastrointestinal tract.

ACTION: The Field trial candidates 75, 82, 87, 90, are to be examined in further dog studies to qualify their safety factors (JRH).

Isopar M systems with $MgCl_2$ are to be tested along with new synthetic oils (JRH).

5. **BIOLOGICAL DATA (JB)**

Since the last meeting 4 Emulsion formulations have been studied in the Glasshouse (82, 87, 89 and 75). The standard JF10991 (26) was also included for comparison. They were compared with standard technical paraquat both with and without Agral. Generally, all the MEF's behaved well as regards herbicidal efficacy although some small differences were observed between species. The primary Emulsion 75 was the best of the group in these studies. Formulations 82 and 87 were equivalent to standard paraquat. Emulsion 89 was better on dicots than grasses but Agral improved the grasses kill. It was agreed that the magnesium formulation be tested and the Diesel-calcium and Isopar M formulation repeated.

6. **SCREENING STRATEGY (MM)**

The strategy of producing a safer, stable dilutable, sprayable and cost-effective Multiple Emulsion was discussed. At the outset of the programme the Toxicological criteria was the most important. This has moved towards other criteria such as sprayability and commerical factors without hopefully losing the necessary degree of safening. At present, dialysis is used as a criteria for likely safening. This correlation is not strong with small values of paraquat leakage but has been useful in detecting toxic, high leakage emulsions. Obviously, better use of this data together with other factors such as a rheology, inversions, herbicidal efficacy and sprayability will improve the screening of new Emulsions.

ACTION: MM to collate information on toxicology, dialysis, biology and sprayability for data analysis.

7. **TRC MEETING**

Final arrangements for the October 10th meeting were discussed. An outline for presentation was suggested.

1.	Introduction	JMF
2.	Recommendations	-
3.	The Business Case	EP/CAS
4.	Formulation Research	THT/CS
5.	Toxicology	JRH
6.	Biology/Spray testing	JB/MP
7.	Patents	JD
8.	Resourcing Level	ALL

8. **NEXT MEETING**

The next meeting of the workgroup will be held on October 27th, 1988 (Entomology Meeting Room, Jealott's Hill).

Jon R Heylings

DR JON R HEYLINGS
BIOCHEMICAL TOXICOLOGY, CTL

CIRCULATION

J M Fua	
W D McClellan	
Th F Tadros	
H Swaine	
M R Parham	
E J T Chrystal	ICI Agrochemicals
D K Lawrence	Jealott's Hill
B Young	
M Moore	
C Sales	
S Hayes	
J Burns	
P K Thomas	
J E Downes	
E Paterson	
C A Spinks	
G M Farrell	ICI Agrochemicals
G A Willis	Fernhurst
P J Bramley	
P Slade	
J R Heylings	
L L Smith	
I Wyatt	
R C Scott	CTL
M J Farnworth	
R S Morrod	
S E Jaggers	

JDQBCMISC

re PQ

16 NOV 1988

PSAC
PARAQUAT STRATEGIC ACTION COMMITTEE

MINUTES OF THE TENTH MEETING OF THE ABSORPTION OF PARAQUAT - SAFER FORMULATION WORKGROUP HELD ON 27TH OCTOBER 1988 AT JEALOTT'S HILL

Those present: J M Fua - Chairman

Th F Tadros	)	
C G Sales	)	
P K Thomas	)	
S E Hayes	)	Jealott's Hill
M Moore	)	
J Burns	)	
B Young	)	
E Paterson	)	Fernhurst
C A Spinks	)	
J R Heylings	)	CTL

1. FEEDBACK ON THE TRC (JMF)

There was general agreement from the five members of the Workgroup who attended the 10th October TRC that the meeting had gone very well. All our recommendations were met with full approval, in particular, the facility to utilize at least 12 Field Trials next year.

Certain issues discussed at the TRC included the cost of B246, the nature of the oil and the final paraquat concentration of the product.

(i) Cost of the B246 Polymer

The forecasted cost of a Multiple Emulsion Formulation (MEF) is almost entirely based on the cost of the primary emulsifier B246. This is an ICI polymer and it is expected that initial costings exceed a final tendered price. Furthermore, it may be possible to reduce the concentration of B246 in the Emulsion by 0.5-1% without altering any of its properties.

(ii) Nature of the oil

The favourite candidate at the moment is Diesel oil. Obviously a Soya oil product would be more suitable for EPA approval but there are major differences in toxicology of the MEF when such alterations are made. We are investigating other synthetic oils at the moment in an effort to replace Diesel. Territorially, introduction of a Diesel-based MEF to the Far East is less of a Regulatory problem than say the USA.

(iii) Final PQ concentration

Throughout the programme it has been agreed that a commercial MEF is going to be a 100g/l or 10% paraquat product. Higher strength MEF will be more difficult to prepare and dilute. Furthermore, certain territories would probably never allow a return to 20% formulations.

2. NEW MULTIPLE EMULSION FORMULATIONS (CS, SH, PT)

(i) Diesel Oil Formulations

The calcium (82) and magnesium (90) diesel systems have been stored at 50°C for 3 months. There were no problems associated with the dilution of the MEF's after this time. The present problem is to overcome the coagulation which occurs following dilution. Addition of PEG 200, 600, kelzan, urea, sucrose, rhodopol etc. to the internal phase to reduce the osmotic influence of $PQCl_2$ is being investigated to reduce this coagulation. Furthermore, alteration of pH in both phases is being studied. This will alter the solubility of the MEF components. Other ways of approaching the problem are to introduce a charge on the Emulsion droplets using anionic/cationic surfactants or insoluble salts.

(ii) Isopar/Synthetic Oil Formulations

Progress has been made in optimizing the Isopar M system by varying the magnesium molarity. The dialysis figures still do not predict the toxicology very well since the least toxic Isopar MEFs containing 1.75-2M $MgCl_2$ are not the lowest dialysis figures. Similarly, with the Exxol/Escaid mixtures a 3:1 ratio was least toxic and had a 7% paraquat leakage. Improvements to reduce flocculation are being studied using kelzan, PVA + NPE 1800 at the moment.

(iii) Twin Pack/Primary Emulsions

The formulation of a high strength (200g/l) paraquat Primary Emulsion is being pursued. Ether sulphate improves the properties but ease of dilution with a separate external phase is still a problem. A switch to another polymer, B261 improves rheology and aids dilution of the secondary. This area of producing a twin-pack 200g/l Primary Emulsion will be continued until the end of 1988.

ACTIONS: Formulation Group to continue research to optimize the Diesel, Isopar M and Exxsol/Escaid systems. High strength Primary Emulsions to be pursued at least until the end of the year.

3. TOXICOLOGY (JRH)

(i) Diesel Systems

At the last meeting Formulation 90 (B246/Diesel/NPE1800/1.5M $MgCl_2$) had been identified as our most promising MEF. A study was undertaken to find the optimum Mg concentration over a range of 0.75-2M $MgCl_2$. There was a definite improvement in safening with increasing Mg molarity across formulations containing 0.75, 1 and 1.5M with LD50 values of 150, 200 and >250mg/kg respectively in rats. Interestingly, high molarities (2M $MgCl_2$) reduced the safening slightly. It would be of interest to study extreme ranges eg. 0.5 and 2.5M MgCl to confirm this relationship. A repeat batch for Formulation 90 (batch 4) gave identical results to batch 01 despite differences in formulation age. Thus, LD50 for each was around 250mg/kg in rats.

Formulation 90/01 was tested in dogs at 32mg/kg. There were no signs of toxicity and AUC values were low (mean = 28μg/ml.hr) for this dose level. Thus, an intrinsic safety factor exceeding 4-fold has been identified with this MEF. The formulation is scheduled for 48mg/kg in November.

(ii) Isopar M/Synthetic Oil Systems

Six new Isopar M MEF's have been evaluated in rats with $MgCl_2$ replacing NaCl in the external phase. As found with Diesel - MEF's, changing to this new electrolyte has safened the more "sprayable" Isopar MEF. LD50 has risen from 150mg/kg with NaCl to values above 200mg/kg with 1.75 or 2M $MgCl_2$. Isopar M systems have always proved more toxic than Diesel systems in dogs. We have chosen our safest Isopar M/$MgCl_2$ formulation in the next dog study.

The use of the 'synthetic' oils Exxsol and Escaid has given an interesting profile of toxicity. A ratio of 3:1 (Exxsol:Escaid) proved least toxic to rats (LD50 >200mg/kg) and were generally less toxic than Isopar M systems. The electrolyte was switched from Na to Mg and the safest example, formulation 102 containing 1M $MgCl_2$ was non-toxic to dogs at 16mg/kg. The molarity of Mg has now been optimized at around 1.75M $MgCl_2$ and will be tested in dogs this month at higher dose levels.

ACTIONS: JRH to assess the relative toxicity of the Diesel, Isopar and synthetic oil systems in the dog.

4. SPRAYABILITY (BY)

None of the new formulations such as the Diesel/$MgCl_2$ System (90) has been tested for sprayability. This area is resource limited but has now been highlighted as an important area to develop methods of evaluating sprayability of new Emulsion Formulations. To this end a new member of the Group (Tim Bird) has been brought into the team and will look at this issue. In particular, new sensible tests need to be developed. They should also have a different emphasis eg. Knapsack versus recirculator.

ACTION: BY to investigate methods of improving the selection of sprayable Emulsions.

5. WEED SCIENCE (JB)

Since the last meeting three Emulsion formulations have been studied in Glasshouse trials. These were Emulsion 90 which was estimated to be more than one month old. Also Emulsion 102 (1M $MgCl_2$ Exxsol/Escaid system) and 106 (2M $MgCl_2$/Diesel system). A surprising result occurred with Emulsion 90 in that it gave a poor kill at the 100 level but was as good as the standards at 200 and 400. The other magnesium systems gave adequate herbicidal efficacy. Considerable debate ensued on the reproducibility of the Glasshouse trials and just how much use they are to distinguish between formulations. The major problem appears to be the lack of slots available to properly co-ordinate work between Formulation and Weed Science Sections. It was agreed that the poor efficacy of Emulsion 90 at the low

level should be resolved to determine if ageing of the Emulsion contributed to this result. Further action is already in progress to address the issue of storage stability in Field Trials and Toxicology.

Manpower in Weed Science is clearly limiting the number of studies available for the Emulsion Programme. Unless this is satisfactorily resolved and there is someone exclusively dedicated to Emulsion testing, we can only rely on Field Trials to assess herbicidal efficacy.

ACTIONS: JMF to discuss the resource issue with WDM.
Formulation 90 to be tested fresh, 1 month old and 3+ months old to determine herbicidal efficacy, and batch to batch variability (TFT).

6. REPORTING FORMAT/CRITERIA (MM)

Optimal use of our data is very important in assessing trends and how each parameter relates to one another. Data from toxicology, dialysis, herbicidal efficacy is being collated. A test of sprayability would considerably enhance the comparison of Emulsion formulations. No pattern between dialysis and toxicology is clear and herbicidal efficacy data was considered to be quite variable.

ANY OTHER BUSINESS (ALL)

The issue of packaging was discussed. For example if we developed a Twin-Pack Primary Emulsion System, how feasible are packs within packs. It was agreed that CAS and BY should discuss this issue.

Dr Jon R Heylings
Biochemical Toxicology, CTL

CIRCULATION

ICI Agrochemicals, Jealott's Hill

J M Fua
W D McClellan
Th F Tadros
H Swaine
M R Parham
E J T Chrystal
D K Lawrence
B Young
M Moore
C G Sales
S E Hayes
J Burns
P K Thomas
J E Downes

ICI Agrochemicals, Fernhurst

E Paterson
C A Spinks
G M Farrell
G A Willis
P Slade

ICI Central Toxicology Laboratory

J R Heylings
L L Smith
I Wyatt
R C Scott
M J Farnworth
R S Morrod
S E Jaggers

CH/BMISC2
11.11.88

COMPANY SECRET

This document has been circulated by

PSAC

PARAQUAT STRATEGIC ACTION COMMITTEE

MINUTES OF THE TWELFTH MEETING OF THE ABSORPTION OF PARAQUAT - SAFER FORMULATION WORKGROUP HELD ON 24TH JANUARY 1989 AT JEALOTT'S HILL

Those present: H Swaine - Chairman

Th. F Tadros)
M R Parham) Jealott's
B Young) Hill
G G Sales)
M Moore)

J M Fua)
E Paterson) Fernhurst
J Verity)

J R Heyings) CTL
L L Smith)

1. MATTERS ARISING

There were no matters arising and the Minutes of the meetings held on October 27th and December 15th were accepted.

2. CHAIRMANSHIP OF THE WORKSHOP

Harry Swaine will be the new chairman of the technical workgroup. He thanked Jee Mok for his efforts in 1988 during which time significant progress had been made in the Multiple Emulsion programme. It was also agreed that Jon Heylings will continue to minute and report the meetings of the workgroup.

3. UPDATE ON FORMULATION PROGRESS (CS/Th.F.T)

(i) Flocculation

The major aim of the formulation group has been to reduce the flocculation resulting from dilution of the Multiple Emulsion Formulation (MEF) in water. One key feature here is to devise a test which assesses the degree of flocculation so that only the most suitable systems are evaluated at CTL. A measurement of % creamed height following dilution may give an indication of the degree of flocculation. Various types of profiles of % creamed heights have been obtained by minor changes in the MEF composition or process. Collaboration with University College London may provide a new optical method for flocculation monitoring.

cont'd .....

A wide variety of components of the MEF have been varied in order to reduce the % creamed height to a minimum. These include different internal and external phase additives, altered pH, reduced secondary volume fractions, temperature and paraquat concentration. The most predominant effects occurred with reduced secondary volume fraction, increased NPE 1800 or with Sucrose, PEG 200 and propyleneglycol added to the internal phase.

(ii) Nature of the oil

It appears that the nature of the oil in the MEF is still crucial. Soya bean oil systems produce less creaming than diesel oil but invariably have higher paraquat leakage characteristics and are more toxic. A number of new oils can be tested such as mineral, white, sesame seed, sunflower, cotton seed, castor, pine, silicone, linseed and rapeseed oils to hopefully identify an alternative system which is as safe as previous diesel MEF's and has acceptable dilution/spray characteristics. Furthermore, the diesel oil additives (antiwax, dispersants an viscosity modifiers) will be evaluated in case they contribute to the general properties of diesel-based MEF's.

(iii) Scale-up experiments

An important part of the programme is to investigate how robust the system is when scaled up from 200ml to 10 litres. Large batch volumes will be needed for the Field trials and sufficient will have to be made for storage testing and toxicology testing. Three different MEF's have been scaled up to 10 litres. These include the diesel systems 90 and 121 and the exxsol/escaid system 132. The main problems with scale up have been ensuring an effective initial dispersion of the primary emulsion and avoidance of shear-induced flocculation. The size of the droplets in the Emulsion are critical to its stability and this has shown to be important in the degree of safening the MEF exhibits in CTL rat studies. Once optimized with respect to a number of variables, samples have been stored at -20-50°C. There have been encouraging results to date with little change in the 3 Emulsions from -10-50°C. In order to improve the process, various chemical engineering aspects of process have been discussed. Insertion of baffles in the mixing vessel will hopefully create turbulence and remove stagnation points. The best and most consistent solution will be the use of static mixers which John Middleton (Process Development, Runcorn) is to design.

ACTIONS: The process will be optimized to reduce flocculation as much as possible. Examples of scaled-up (10 litres) MEF's will be sent to CTL for toxicological evaluation (CS/Th.T).

The nature of the flocculate and improved methods of its measurements should be investigated (CS/Th.T).

cont'd .....

4. UPDATE ON TOXICOLOGY (JRH)

CTL Rat Studies

(i) Diesel MEF's

Since the meeting at the end of October 1988, a further 27 new Multiple Emulsion Formulations have been tested in rats. Relative degrees of safening have been determined using 3 dose levels with 5 animals at each dose. Formulation 90 has consistently given us an acceptable degree of safening. Two separate batches (01 and 04) gave oral LD_{50} values around 250mg/kg. This compares with a contemporary Gramoxone control of 100mg/kg. Formulation 121 which differs from 90 only by reduction of the secondary volume fraction has been extensively studied in the rat. The first batch (01) prepared to 200ml also gave an LD_{50} of 250mg/kg. However, subsequent batches (02-07) made to different volumes and by different processes gave LD_{50} values ranging from 150-200mg/kg and were thus inferior systems. In particular, batch 02 was significantly more toxic than all previous batches of Formulation 121. This is unlikely to be poor reproducibility in the rat test, since 121/02 also gave very high plasma values in the dog at 16mg/kg (see below) and is likely to be an unstable batch. (Note: since this meeting a further batch of this MEF 121/08, made up to 10 litres, has given an LD_{50} in excess of 200mg/kg, 13 out of 15 animals surviving 150-200mg/kg doses).

(ii) Synthetic oil MEF's

As an alternative to the diesel system, mixtures of Exxsol and Escaid oils have been tested. Such systems with NaCl in the external phase consistently gave LD_{50} above 150mg/kg. On switching to $MgCl_2$ LD_{50} values increased to around 200mg/kg and a ratio of 3:1 Exxsol:Escaid showed the best safening properties. Further optimization was then made with respect to the $MgCl_2$ concentration. This was best at 1.75M $MgCl_2$ (Formulation 115/01). More recently the secondary volume fraction has been varied and the MEF scaled up to 10 litres. Currently Formulation 132/02 has an LD_{50} of 200-250mg/kg which is as safe in rats as our best diesel systems.

(iii) Isopar and Soya oil MEF's

Four MEF's based on Isopar M have been examined. They were based on $MgCl_2$ with various primary volume fractions. Formulations 129/01 and 130/01 have LD_{50}'s in excess of 200mg/kg, which is an improvement over all previous Isopar M types. A Soya oil MEF (133/01) was comparatively more toxic with an LD_{50} around 150mg/kg and remains our least promising oil type.

cont'd .....

(iv) Miscellaneous MEF's

A further 10 MEF's based on diesel oil but with a number of new variables such as changes in pH, sucrose, PEG, NPEC etc. included have been studied. The most promising of these were 119/01 which contains 20% PEG 200 (internal phase) which gave an LD_{50} around 300mg/kg. Also Formulation 127/01 containing 0.5M sucrose (internal phase) which also had an LD_{50} close to 300mg/kg. If such MEF's pass the other criteria of flocculation/stability etc., they will be pursued in dog studies.

CTL Dog Studies

(i) Diesel MEF's

Since the October 1988 meeting several more dog studies have examined in more detail the likely safening properties of our best MEF's. Formulation 90 was progressed to 16, 32 and 48mg/kg. Plasma paraquat AUC values increased from 13.7±4, 28.4±2.4 to 34.2±9.4µg/ml x hr. respectively. AUC values in excess of 45µg/ml x hr. usually result in toxic signs. One animal at 48mg/kg did not recover fully and was terminated resulting in this dose becoming near LD_{50}. All other animals at these three doses were symptom-free and remain healthy. Thus, Formulation 90/01 has a 4x intrinsic safety factor.

Formulation 121/02 has been tested at 16mg/kg in 3 animals. High plasma paraquat levels resulted in an AUC of 63.7±7.1µg/ml hr. and loss of one animal. Formulation 121/02 was therefore offering no significant safety margin. As described above there are probably process difficulties with such MEF systems. Only when this is optimized and rat studies show clear safety levels will this MEF be repeated in the dog.

(i) Synthetic oil MEF's

The Exxsol:Escaid MEF 102/01 was tested in dogs at 16mg/kg and gave no toxic signs and an AUC value of 26.3µg/ml x hr. Further modification of this system resulting in Formulation 115/01 was tested at 24mg/kg. Again there were no problems and the AUC was calculated at 22.1µg/ml x hr. To date, we have at least an intrinsic 3x safety factor with such systems.

General Comment

Both the Diesel and the Exxsol:Escaid systems are being made on a larger scale for hopeful Field Trial testing. Until the process and final composition of these formulations has been finalised the rat test will be used to distinguish the differences in toxicity of the MEF's and the final version will then proceed to the dog.

ACTION: The relative toxicities of larger scale preparations MEF's will be examined firstly in rats and finally in the dog to establish safety margins (JRH).

cont'd .....

5. SPRAYABILITY

No data was presented on sprayability of MEF's. During discussion it was suggested that if the stored samples of MEF's met the criteria of dilution and % creamed height that they should be sent to Brian Young for sprayability testing. Concern was expressed by Martin Parham that it is not just the amount of flocculation whch is important in the assessment of sprayability but the nature of the flocculate. For instance, a large amount of soft flocculate may be less of a problem than a small amount of hard material. It was agreed that we should look at this in more detail.

Another issue which was raised concerned the use of Agral with MEF systems. Previous Field trials with Formulation 90 suggested that there were no flocculation problems when used with Agral. Although the aim of the workgroup is to provide a "gold" standard MEF which can be used in all situations as a single pack, in reality certain territories always use extra surfactant and some only use certain types of spray equipment. The commercial requirements should be spelled out more clearly in order for the group to direct themselves to a specific end point.

ACTION: The territories to which the MEF's are aimed should be clarified with respect to use of Agral and use of different spray equipment (EP/JV).

6. FIELD TRIALS

Field trials are planned for 1989 with 2 MEF's. In order to select the best systems a number of hurdles have yet to be overcome. As regards the formulation, the major effort is to produce a satisfactory scaled-up volume which will provide enough material from one single batch to cover the storage testing, toxicity testing, spray testing and toxicology as well as the trials themselves. The probable candidates will be variants of Formulations 121 (Diesel) and 132 (Exxsol/Escaid). However, before a decision is made on these trials the group felt that the following criteria should be met:

THE SAME BATCH OF MULTIPLE EMULSION FORMULATION SHOULD HAVE ACCEPTABLE STORAGE, DILUTION, SPRAY AND TOXICOLOGICAL PROPERTIES PRIOR TO FIELD TESTING.

cont'd .....

7. **MEETING DATES**

The dates of the meeting of the Multiple Emulsion Workgroup during 1989 have been circulated. They are scheduled as follows:

Tuesday 11 April
Tuesday 20 June
Tuesday 12 September
Tuesday 7 November

All Technical meetings will start at 1.00pm in the Ento Meeting Room at Jealott's Hill.

Dr Jon R Heylings
Biochemicl Toxicology, CTL

CIRCULATION

ICI Agrochemicals, Jealott's Hill

H Swaine
W D McClellan
Th F Tadros
M R Parham
E J T Chrystal
D K Lawrence
B W Young
M Moore
C G Sales
J E Downes
D W R Headford

ICI Agrochemicals, Fernhurst

J M Fua
E C Paterson
C A Spinks
G M Farrell
G A Willis
P Slade
J Verity

ICI Central Toxicology Laboratory

J R Heylings
L L Smith
I Wyatt
R C Scott
M J Farnworth
R S Morrod
S E Jaggers

JMPBMISC3 (TWMTGPARA)
3.2.89

→ RCS.

Dr. L. L. Smith

MINUTES OF PSAC TOXICOLOGY SUB-COMMITTEE MEETING
Fernhurst, 11 February 1991

PRESENT :	G A Willis	(Chairman) -	PSS
	J M Fua	(Secretary) -	RAD
	R A Morrison	-	Herbicides, Products
	N N Sabapathy	-	PSS
	J Heyling	-	CTL
	J D Pidgeon	-	Development
	A J Starling	-	Development
	G W Allen	-	Public Affairs
	M R Thomas	-	Public Affairs
	G R Farrell	-	BMW (Part-time)

The proposed agenda was accepted by all those who were present - Appendix I.

1. SPRAY DILUTION RECOMMENDATION FOR PARAQUAT

At the 30 March 1990 meeting, concern was expressed that the 1:40 solution was found to be unsafe following field operator-exposure studies conducted in Malaysia. That meeting also noted that to spray at these concentrations, knapsack sprayers have to walk at unrealistic speeds when using flood-jets.

Mike Thomas stated that LV nozzles are being used with knapsacks in parts of Africa and Latin America using spray volumes of 50 l/ha. However in most LDCs farmers are using higher than 1:40 dilutions but probably less than 1:100.

The committee made the following proposal :

"A minimum dilution of 1:100 should be recommended when using hand-held equipment. For those territories that wish to use higher concentrations, the local company must review its merits for so doing on an individual case basis."

The Committee noted that 1:40 dilution is deemed acceptable for tractor-mounted sprayers.

Label recommendations should highlight linkage between higher volume and greater bioefficacy.

ACTIONS : **1.1 GRF/NNS/GA to follow up on basis of product safety, country specific needs and product stewardship in implementing the above proposal.**

1.2 MRT to contact Malcolm Ogilvy (PAS) to :

a) liaise with sprayer/nozzle manufacturers to obtain their recommendations on nozzle for use with paraquat.

b) establish the distribution of low volume nozzles by territories.

1.3 GWA/PSS to ensure that paraquat is not recommended with CDAs as it will be impossible to enforce the wearing of protective clothing.

1.4 MRT/NNS should establish the extent of paraquat usage in amenity situations where odd equipment(s) and application methods are used.

2. CONTAINER SIZE AND LABELLING

The Committee noted that paraquat business is being conducted in many parts of the world without due adherence to FAO Code of Conduct on Labelling. R Morrison stated that the circumstances for such practices are very wide-ranging; many of which are beyond ICI's control. The meeting emphasised that in the event of any accident with paraquat, ICI will be implicated irrespective of whether the material is ICI's or not.

ACTION : GWA/RAM to look into minimal labelling for bulk drums; extent of decanting and re-packing at distributor/user level and re-use of paraquat containers.

3. MAGNOXONE

Amanda Starling presented the development time-table for "Magnoxone". Patent publication is expected end-1991. The programme for 1991 is as follows :

a) prepare stable formulation
b) confirm bioefficacy and tox advantage
c) if a) and b) above are fully satisfied, test market "Magnoxone" in Surinam by Mid-1992.

NNS felt confident that, due to her small population (0.5 million), and special use in rice and vegetables, stock management can be effectively handled in Surinam.

There have been some queries from territories on the availability of "Magnoxone".

ACTIONS : 3.1 JDP/AJS/ to respond appropriately to territorial queries - essentially it is not yet in development.

3.2 NNS to start planning by mid-1991 for eventual field study in Surinam in mid-1992.

3.3 JDP to liaise with NNS in respect to concurrent bioefficacy monitoring.

4. THICKENED FORMULATIONS

Paraquat is facing a potential ban in Hungary due to the high incidence of paraquat suicides in the country. Whilst Hungarian authorities responded favourably to the Weedol formulation, this product is less suited for larger-scale use on state farms. The French thickened formulation would be more suitable and is being considered for Hungary.

ACTION : AJS/J Heylings to arrange for the Hungarian thickened formulation to be tested at CTL.

5. UPDATE ON GI TRACT UPTAKE RESEARCH

Jon Heylings explained the background to the discovery of the effectiveness of the magnesium salts in 'safening' paraquat during development of the paraquat multi-emulsion project. $MgSO_4$ was effective even when added directly to aqueous paraquat product (Gramoxone). It is used as a purgative at 1.5M, eg Epsom Salts. Magnesium trisilicate $Mg_2Si_3O_8$ on the other hand is used in pharmaceuticals as an antacid. $Mg_2Si_3O_8$ reacts with the gastric acid in situ to produce a gel in the stomach. Combining $MgSO_4$ and $Mg_2Si_3O_8$ we could gain a 5X safety over paraquat alone. Secondly, by increasing PP796 emetic to 2.4 mg/l in Gramoxone will further increase safety by 5X. Therefore by combining the Mg-salts with emetic, a 10-15X safety can be achieved. Proposed composition of "Magnoxone" is presented in the table below.

Proposed Composition of "Magnoxone"

Paraquat dichloride	200g ion/l
PP796 emetic	~~2.4 mg/l~~ → should be $1.5\ g\ L^{-1}$ (altered at meeting 7.3.90)
Mg-trisilicate	100 g/l
Mg-sulphate	100 g/l
Kelzan	3 g/l

Safening is achieved by a combination of increased emesis of the 'gelled' Mg-salts + Pq, purgation of any material entering the GI tract, and reduced uptake due to Mg blocking uptake sites in the gut.

Jon Heyling also reported that the French thickened formulation of paraquat has 10X safety factor.

GRF asked what ethical position ICI should now take in light of the present evidence that PP796 at 0.5 mg/l is insufficient in Gramoxone, whereas 2.4 mg/l will be 'safer'. The Committee noted that this issue exists only if major fatalities are due to accidental paraquat poisoning as it will not address the suicide problem.

Due to the limitation of time, the meeting adjourned with the proposal that it reconvene on 7 March to review the higher emetic Gramoxone option and to discuss the remainer of the agenda item.

COPIES TO :

Those present+
L L Smith CTL
H Swaine Formulation, Jealott's Hill

JMF/BJS/MINS1
18 02 91

PSAC

MINUTES OF PSAC TOXICOLOGY SUB-COMMITTEE MEETING
7 March 1991

Present : G A Willis (Chairman)
J M Fua
R C Scott
J R Heylings
N N Sabapathy
G W Allen
A J Starling
M Thomas
A Calderbank

1. **MINUTES OF MEETING OF 11 FEBRUARY AND ACTIONS ARISING THEREFROM**

Minutes accepted with corrections to the value of PP796 to read g/l and not mg/l.

2. **EMETICS ISSUE**

Discussions centred around the question of whether the number of fatalities from paraquat poisoning can be reduced by increasing the concentration of emetic, PP796, in aqueous formulations of paraquat. NNS estimated that over 70% of all cases of accidental ingestion of paraquat survived, and the emetic contributes to this survival. NNS does not believe that increasing PP796 in 'Gramoxone' will reduce fatalities from suicide significantly, as doses ingested are 10-20 times the lethal dose. After much debate on the ethical issue of "being seen" to do something about reducing fatalities, the meeting adopted the following position:

'Gramoxone' has a proven track record of occupational safety, when used as directed and in accordance with stated handling precautions. We are not in the position to manage suicides - there are many other ways to address this problem other than increasing the emetic, eg reducing the strength has been suggested/restrictions on availability.

The Sub-Committee agreed that any change should be materially significant in reducing suicides/fatalities. Therefore, the process of evaluating 'Magnoxone' or any other "safer" paraquat formulation should be gone through. Until this has been properly evaluated, we are not yet in the position to make recommendations for increased emetic. However, AJS felt that if we consider the emetic option, it is important that the Sub-Committee is fully behind the proposal to help the "Business" move forward with the plant capacity for PP796.

3. **POISONING STATISTICS (NNS)**

We have collected data from a number of countries, which included Malaysia, Fiji, Surinam, Hungary, etc. The number of incidences of paraquat poisoning has plateaued since 1987/88. Perceptions in paraquat safety has shifted to the occupational area in recent years. The numbers are declining in the UK and Hungary, but increasing in some Latin American countries, which may be due to socio-economic pressures in these countries.

ACTION : NNS to make formal presentation at next Sub-Committee meeting

4. **OCCUPATIONAL SAFETY**

The perception of paraquat toxicity associated with suicides is now increasingly having the effect of causing concern of its safety in occupational use. Safety in occupational use has been raised in many countries at various levels. In some countries, legislation is being amended to reclassify paraquat into categories that would make its use conditional (as specified in the amendments). Equally, there are countries that want to implement restrictions of use (following EPA regulations).

ICI has put up strenuous arguments in favour of the commendable safety record in occupational use of paraquat. It has also embarked on major stewardship programmes - including education and training - in many countries to enhance the safe use of not only paraquat, but pesticides in general. Positive contributions such as this, combined with the benefits of paraquat to agriculture, has stood in good stead in the defence of our position.

Continued support to authorities and a positive presence in our operating countries is a vital proactive position that we must continue to take in order to effectively rebutt the numerous allegations made against paraquat.

ACTION : NNS to prepare updated report on paraquat poisoning

5. **TREATMENT OF PARAQUAT POISONING BOOKLET**

Degree of success of recovery from paraquat poisoning is correlated to the level of effort employed in treatment within the first two hours by medical staff. Jon Heylings proposed that purgation with non-irritant material should be emphasised in the booklet.

ACTION : a) NNS/GWA and supported by Dan Ashdhown to ensure that all NCs have sufficient stocks of Fuller's Earth and booklets.

b) NNS/Jon Heylings to update booklet

6. LEVEL OF STENCH

Stenching agent has caused resentment amongst applicators and dealers (during storage) in some countries. NNS/AJS have recently sent questionnaires to over 130 countries to check:

- concentration of stenching agent in their paraquat formulations/ products
- whether they have experienced problems

Questionnaire attached. (Appendix 1).

7. BIOLOGICAL MONITORING

A Calderbank proposed that the "Paraquat Test Kit" be introduced to monitor levels of exposure in operators/sprayers. The kit can qualitatively detect paraquat in the urine (down to 1-2 ppm).

RCS and NNS expressed concerns and have reservations to wide introduction of the kit in the field. There is tremendous potential for errors to occur and wrong interpretation, due to the lack of clinical controls in handling urine samples.

ACTION : Committee to await outcome of the actions agreed at previous meeting on survey of low volume/high concentration (1:40) spraying of paraquat

8. ANY OTHER BUSINESS

8.1 US LEGAL RULINGS

GWA stated the case of legal action being taken by a LDC in the US Court involving EPTC where the ruling was awarded in favour of the Plaintiff. What is the potential for paraquat cases in LDCs being brought up in the US Courts?

ACTION : NNS to check with M Herlihy what is the present situation of court cases in the USA

8.2 PARAQUAT STUDY IN COLUMBIA

An IDRC funded study, conducted in Columbia, on the occupational hazard of paraquat use, has been published in "Pesticide Outlook". The study was conducted in a pottery making area and concluded that paraquat use has an influence on the incidence of respiratory disorders. NNS stated that the study has major flaws due to:

- poor protocol
- vague definition of "test" population
- no quantification of exposure levels
- method of test too general, eg lung function
- only questionnaire survey

The Colombian authorities have "distanced" themselves from this study.

ACTION : PSS to issue a note to clarify the above situation within the business

9. NEXT MEETING

The next meeting is scheduled for July.

JMF/EJH.
MINS1
Misc 10
9/4/91

From

P J BRAMLEY
Herbicides Management

To

See Attached

ICI Plant Protection Division
Fernhurst
Haslemere Surrey GU27 3JE

Telephone Haslemere (0428) 4061 Switchboard
Redacted - EU PII Direct line
Telex 858270/858512
Telegraphic Plantector Fernhurst Telex
Facsimile Haslemere (0428) 52922

SEJ 19.1

Copies to

Redacted - EU PII

Your ref	Our ref	Tel ext	Date
	PJB/WJM	Redacted - EU PII	11 February 1986

MINUTES OF THE SECOND MEETING OF THE PARAQUAT STRATEGIC ACTION COMMITTEE (Held on 24 January 1986)

I enclose a copy of the above for your interest. It is proposed to hold the next formal meeting in early April 1986. I will issue a meeting date and detailed Agenda nearer the time. Ongoing developments in this area will continue to be circulatd as appropriate.

Peter Bramley

Enc

From Dr Stuart Jaggers	COPY
For Action	
B/Forward	
For Info	
File PQ	

Paraq Strat. Act Com

PSAC.

Circulation

Dr D Cornthwaite	: Directorate
Mr J R Finney	: Directorate
Dr J T Braunholtz	: Directorate
Mr J C Francis	: WER
Mr T C Frears	: EMA Region
Mr D F Manning	: FEP Region
Mr R A Woods	: Americas
Dr A K Stapleton	: Herbicides
Dr D H Brooks	: Development Department
Mr C A Spinks	: Development Department
Mr C S Major	: Public Affairs
Dr T B Hart	: PSRG
Mr G A Willis	: PSRG
Dr L L Smith	: CTL
Mr D J Viney	: Product Supply Department
Mr H Swaine	: Jealott's Hill
Mr M J Edwards	: Yalding
Mr P J Bramley	: Herbicides

MINUTES OF THE SECOND MEETING OF THE

PARAQUAT STRATEGIC ACTION COMMITTEE

COMPANY SECRET

Held at Fernhurst on Friday, January 24, 1986

Present:-

Dr A K Stapleton (Chairman)	: Herbicides
Dr D H Brooks	: Development Department
Mr C A Spinks	: Development Department
Mr C S Major	: Public Affairs
Dr T B Hart	: PSRG
Mr G A Willis	: PSRG
Mr A J Robinson	: Americas Region
Mr D F Manning	: FEP Region
Mr T C Frears	: EMA Region
Mr A G Potter	: WER Region
Dr L L Smith	: CTL
Mr D J Viney	: Product Supply Department
Mr P J Bramley (Secretary)	: Herbicides

1 PARAQUAT REGULATORY POSITION

1.1 West Europe

GAW presented a summary of recent developments in Switzerland, Netherlands, West Germany, Italy and Scandinavia. These had been discussed at the Regulatory Fly-In held at Fernhurst in mid-January. Details are attached in Appendix 1.

1.2 European Parliament

CSM indicated that representations by the chemical industry against the recently drafted 'Resolution on agriculture and the environment' had succeeded in removing named agricultural chemicals (including paraquat) from the text and deleterious references to the 'Dirty Dozen'. The Environment Committee was still considering the document which will be voted on shortly.

1.3 Japan

DFM summarised developments since the last meeting in November. It now looks as if the pro-dilute, 5% 'Gramoxone' lobby in Japan was not succeeding and that dilute 'Preeglox L' would be launched in early June 1986. The registration package should be ready by end-March 1986. 'Gramoxone' sales were due to commence in Japan from late January 1986 once the restrictions/monitoring on availability had been instigated. The forthcoming visit of Professor Naito (who is involved with the SDS Biotech 'paste-like' granule) and the Guy's Hospital Paraquat Poisoning Symposium pose potential problems in the defence area. Both are being handled with the appropriate PPD resource inputs. CSM/GAW will produce the note on the Japanese situation for internal ICI circulation once the strategy looks clear.

ACTION : C S Major/G A Willis

2 FORMULATION DEVELOPMENT WORK GROUP

2.1 Solid Paraquat

The proposed two-part work programme for 1986 on solid paraquat was approved. The extra resource needed to meet this programme will be available from end-January 1986 (Appendix 2).

ACTION : WED, Yalding

This programme will cover evaluation of the new SDS 'paste-like' granule under a secrecy agreement. ICI is required to report to SDS by end-March 1986 when the agreement expires.

2.2 Thickened Formulation

The proposed two-part Yalding work programme for 1986 on the thickened paraquat formulation developed by Sopra was discussed (Appendix 3). It was agreed that the evaluation of such a formulation for international use (rather than just for France) was desirable as a means of increasing the 'basket of options' for future product defence and in particular of perhaps defending the 200 g/l strength formulation. However, it was felt that the proposed resource input of 1 man year (largely Experimental Officer effort) may not be appropriate.

ACTION : D H Brooks/D J Viney to review

3 INCREASED EMETIC CONCENTRATIONS

GAW summarised the report of the Work Group (See Appendix 4). It is hoped that France and Japan can be used to test the hypothesis that an increase in the level of emetic concentration above the current 0.5 g/l will lead to a reduction in poisoning mortality rates along the lines indicated in animal experiments recently completed at CTL. LLS indicated that the full CTL reports will be available shortly. Both markets will provide experience from diluted formulations of paraquat. The Work Group is still looking for other suitable 'test' markets so as to ensure a rapid and full data response.

ACTION : Regions to consider

4 GENERATION OF AGREED DATA BASES

4.1 Regulatory

Discussions with PSRG have led to the agreement that the following three areas of work require addressing:-

(a) The parameters to include in the new 'Smart' system, being developed to replace the 'Delta' system.

(b) The checking of the present data base.

(c) Updating of the system.

The following parameters will be included in the new system:-

Chemical name
Trade name
Formulation number
Formulation type and concentration
Country
Regional code
Regulatory status
Restrictions
Submissions date
Registration date
Expiry date
Outlet (crops)
Tolerances
Harvest intervals
Current (yes and no)
Comments (a field for further information)
Notification date

PSRG will have changed to the new system by early February. A copy of the present print-out will be sent to all units for their updating. Within two months, this updated record should be available. PSRG will substantially update the record quarterly by using dedicated contract resource.

ACTION : C A Spinks/M S Thomas by next meeting

4.2 Commercial

Investigation of available Group data on past sales of paraquat indicated that it should be possible to generate sales histories back to 1980 by major formulation by market. This work should be completed in 2-3 months. The key requirement is an agreed Regionally-owned, consistent data base.

ACTION : P J Bramley/M S Thomas

5 SOILS WORK GROUP

On the basis of recent analytical work it is clear that the strong adsorption capacity of some extremely sandy soils and highly organic soils is capable of being exceeded if very high rates of paraquat are applied annually.

This fact, combined with the regulatory action which has been taken over paraquat in West Germany and Holland makes it important that ICI's views on this subject should be clear and explicit.

The key technical facts remain as follows:-

* On contact with soil, paraquat is rapidly and strongly adsorbed to clay minerals. This process deactivates it and renders it biologically inactive.

* Most soils can strongly adsorb and deactivate paraquat residues resulting from hundreds or thousands of normal applications.

* Sands and organic soils have the lowest capacities to deactivate paraquat, but even these soils can deactivate residues resulting from very many applications.

* Long-term field investigations show that paraquat residfues in soil are slowly decomposed.

* The rate of decomposition means that the deactivation capacity of almost all soils can never be exceeded as a result of the prolonged use of paraquat.

* There is no risk that adsorbed paraquat residues will be leached out of the soil, nor displaced by fertilisers or other agricultural chemicals.

* There is no known case where the normal use of paraquat has led to the deactivation capacity of any soil being exceeded, nor where paraquat once adsorbed has been subsequently reactivated.

* Adsorbed paraquat residues are not taken up by crops and have no effect on plants or crop yield. They do not affect earthworms, micro-arthropods or micro-organisms in the soil, nor do they alter the availability of nutrients.

* Adsorbed residues therefore have no agronomic or environmental consequences.

Diquat is also rapidly and strongly adsorbed to clay minerals, however its use pattern and rates preclude the possibility of a soil's strong adsorption capacity being exceeded even on extremely sandy and highly organic soils.

In order to ensure that no problems ever arise as a result of the strong adsorption capacities of extremely sandy or highly organic soils being exceeded, a precautionary statement should be added to paraquat product labels during the normal process of label revision. The Technical Review Committee of 12 July 1985 gave strong support to the recommendation that the Soils Work Group should draft label recommendations covering the further use of paraquat and paraquat mixtures. It was agreed that such recommendations should be produced for wider internal discussion and that the timing of the process would be governed by the regulatory climate in Western European countries.

At subsequent meetings it has been decided that a proposal will be made to the Regions for a 'blanket' statement to be placed on all paraquat and paraquat/diquat mixture labels. Regions will be asked to justify any specific exemptions. The label recommendation for paraquat-only products will be something like:-

'To avoid the possibility of crop damage do not apply more than an average of 3 l of product/ha/year on very sandy or organic soils'.

A draft of such a recommendation will be available in February 1986 and responses from the Regions are planned to be available before end April. Therefore by May 1986 an internally agreed amendment should be available which can then be placed on lables in a timescale appropriate to the regulatory strategies and label reprinting plans for all countries.

The Committee expressed concern at the possible commercial/regulatory implications of such a label recommenation particularly in the current regulatory environment for paraquat.

ACTION : C A Spinks to bring forward specific recommendations to the Committee before finalising

6 OVERALL STRATEGY FOR THE INTRODUCTION OF PARQUAT/DIQUAT MIXTURES

The recent crisis in Japan has thrown into focus the current strategy for introducing paraquat-diquat mixtures as one method of defending the paraquat business in a particular market. In particular it revealed gaps in PPD's data base on acute toxicity of the new liquid formulations and on poisoning case histories. The crisis also highlighted the fact that diquat is now being drawn into the regulatory limelight.

It was agreed that Herbicides Department and Development Department should co-ordinate a review of the overall strategy of introducing these liquid formulations covering:-

* Biological implications and field data base
* Toxicity implications and data base (including current CTL studies)
* Poisoning treatment
* Economic implications (active ingredient, formulation, packaging)
* Diquat toxicological and environmental data base (including soil)

It was proposed to bring this study forward to the next Paraquat Strategic Action Committee meeting.

PJB/WJM ... 11/2/86 ... A 601

APPENDIX 1

CONFIDENTIAL

PARAQUAT REGISTRATION STATUS

As of 21 January 1986

WESTERN EUROPE

FRANCE

In October 1982, the Commission des Toxiques (regulatory committee) recommended that liquid formulations of paraquat should be limited to a maximum strength of 4%. [NB. A 4% liquid product had been on sale already to smallholders and the 20% into main agricultural and horticultural outlets.] The Commission's recommendation came about because of concerns over poisoning incidents, mainly in the French Antilles. The recommendation required the endorsement of several ministries, including the Ministry of Agriculture, before a regulation could be issued. The Ministry of Agriculture has refused to countersig. the proposal so far, on grounds of its present impracticability. Thus GRAMOXONE 2000 has remained on sale. However, in principle (but see below), any new paraquat registrations, whether of ICI or non-ICI products, would have to comply with the 4% proposal. The inclusion of colour, stench and emetic are mandatory.

As a further safening proposal, ICI SOPRA have introduced the French authorities to the concept of a thickened formulation. The SOPRA proposal was to thicken the 20% formulation but initial indications are that the authorities will seek a concurrent reduction in paraquat content to 10-12% (but not down to 4%). Trials using thickened material(s) are scheduled during 1986.

FEDERAL REPUBLIC OF GERMANY

Registrations in the Federal Republic run for a maximum of ten years, after which they have to be renewed if sales are to continue. The registrations for CRAMOXONE, GRAMOXONE S and DUANTI (equals WEEDOL) have thus expired. The authorities have refused to re-register them. The Federal Health Authority (BGA) gave its consent to continued registration, until October 1986, of products containing up to 10% paraquat. However the regulatory agency (BBA) refused to renew registrations "because of the behaviour of paraquat in soil".

At the centre of the dispute between ICI and the authority is the unwillingness of the authority to accept the evidence for the degradation of paraquat in soil in the field. The authority argues that use at the maximum permitted rate for the duration of registrations hitherto has the potential, in extreme cases and in the absence of any degradation, to saturate the deactivation capacity of soils, leading to a potential for residual phytotoxicity, "an imminent hazard" which the authority considers it needs to legislate for. In this process, the authority argues that it cannot differentiate between soil types.

The ICI position is that paraquat residues decline in soil in the field, albeit slowly but nevertheless at a rate which will be sufficient to ensure that an equilibrium is reached between annual addition rate and annual degradation of the paraquat present, before the deactivation capacity is saturated in the overwhelming majority of agricultural and horticultural soils. In extreme cases of peats and of sands of less than 5% clay content, limiting the annual use rate of paraquat would in practice obviate any possibility of the deactivation capacity being exceeded. No practical example has come to ICI's attention where the normal uses of paraquat have led to the deactivation capacity being exceeded

and of consequent residual phytotoxicity.

ICI's objections to BBA about their decision were rejected. Therefore ICI had no option but to take the matter to the Administrative Law Court. The case can be expected to continue during 1986.

Meanwhile registrations of various paraquat:residual mixtures, containing up to 10% paraquat, remain in place. They are scheduled to run until 1990.

THE NETHERLANDS

In 1985 The Netherlands finalised a policy document which decreed that pesticides which are persistent in soil are fundamentally undesirable. This is irrespective of whether or not that persistence is of any phytotoxicological or other ecotoxicological consequence. The availability of (perceived) alternatives needed also to be considered when deciding on the registration/ re-registration of such compounds.

On this basis, the pesticide registration committee (CTB) has formulated a recommendation to the Deputy Minister of Agriculture that registrations of paraquat- and diquat-containing products should not be renewed when they expire in November 1988.

Despite a good technical-level meeting on paraquat and an ICI offer of labelling restrictions to ensure no possibility of the soil deactivation capacity being exceeded even in extreme situations, the committee has stuck to its position. The need of paraquat in Dutch agriculture/horticulutre, and the availability of (perceived) alternatives, will now have an important bearing upon the Deputy Minister's decision.

In 1983 ICI Holland agreed that various municipal uses of GRAMOXONE should be switched to WEEDOL to minimise any possible consequences of humans and pets gaining improper access to the undiluted 20% liquid during use by municipalities.

SWITZERLAND

At the authorities' request, ICI/Maag submitted in April 1985 the standard review of paraquat residues in soil.

In December Maag learned that the Swiss authorities were planning to discontinue all uses of paraquat and diquat because of concerns over soil persistence. A meeting therefore took place between ICI/Maag and the authorities on 7 January.

Although the authorities have reached this view, they have not yet initiated the process which would be needed to give effect to their view. At the 7 January meeting, ICI agreed to make a further submission in February on points of technical detail which arose during the discussion. On the basis of the information provided by Maag, ICI has not identified any use situations which would merit introducing a limitation on use. Nevertheless ICI indicated that it would be prepared to conduct a survey (c/f other WER countries) of residues in any situations which are of particular concern to the authorities and, if the results indicated a need, to volunteer use limitations to preclude the longer-term possibility of residual phytotoxicity. The Swiss activities have been influenced by events in The Netherlands and Germany.

In Switzerland, the authorities decided in April 1985 that the paraquat content of registered products should be limited to 12%, effective from August 1986. This move was initiated in the face of pressure concerning the toxicity of paraquat and its abuse for suicides. Concurrently, Maag will be dropping the trade name GRAMOXONE, and will replace the word paraquat with the systematic chemical name, in an attempt to reduce the identification hitherto with the product amongst those who are considering the act of suicide. The classification system in Switzerland limits the availability of such products, including GRAMOXONE, to bona fide agriculturalists and horticulturalists.

SCANDINAVIA

Denmark introduced a proposal five years ago to re-register all existing products before 1 January 1986. Those which had not been registered under this new scheme by that date would cease to be registered on that date. In April 1983 the Danish regulatory body gave ICI Denmark notice that GRAMOXONE and PRIGLONE (equals WEEDOL) would not be re-registered. ICI Denmark objected. In December 1984 the Appeals Board instructed the regulatory body to reconsider its decision, which it has not yet done. Meanwhile the re-registration process was abandoned in November 1985 and all existing registrations continue without time limit. However it would be naive to think that pressures against continued paraquat registrations in Denmark has subsided in the longer term. In 1983 the regulatory body said that its decision was made mainly because of concerns over toxicity and safety in use. A concurrent and similar decision on diquat was made on environmental grounds. A perceived lack of need of paraquat, and the existence of perceived alternatives, influenced the 1983 decision on the compound. The regulatory body is expected to look again at paraquat in the second half of 1986. It would not be surprising if they then take up issues of soil persistence (c/f Holland and Germany).

In view of official concerns over the toxicity of paraquat, ICI voluntarily withdrew GRAMOXONE registrations in Sweden, effective 31 December 1983, in the understanding that a solid formulation (c/f WEEDOL) would be registered in its place (NB. By many European standards, the Swedish uses would have been classified as smallholder.) In the event, the authority refused to register any new formulation of paraquat, on the grounds of inherent toxicity and lack of need, ie perceived alternatives. There is no effective appeals procedure in Sweden.

In Finland, the Pesticide Board, mainly on advice from the Board of Health (Ministry of Health) have cancelled the acceptance and import of GRAMOXONE in Finland. Registration continues until August 1986, but obviously refusal to re-register is the likely outcome. Consequently ICI can no longer export GRAMOXONE to Finland, but can continue to sell the product. The Pesticide Board's decision is based on the 'toxicity of paraquat', although there have only been 2 suicide deaths in Finland in 20 years and no fatal accidents or problems with use of the chemical. ICI has appealed against this decision, through the distributor, Berner Osakeyhtio, and a decision on that is awaited.

Registrations in Norway are due to expire in 1986 and re-registration was applied for recently, with no reaction at this very early stage.

ITALY

The authorities called in an up-to-date submission of the compound in 1985. The data are entering the re-evaluation process now. At this very early stage, there are no indications of any issues arising, nor of their consequence.

SPAIN

The Authority has decided to conform to EEC registration standards by 1 January 1986 when Spain enters the EEC. They have decided that because paraquat is in the most poisonous class in most EEC countries, it should similarly conform in Spain. However, the fourth class category in Spain will restrict application to approved contractors and damage our sales. We have agreed to re-submit a paraquat dossier to obtain a proper review early in 1986.

UK, IRELAND, GREECE, AUSTRIA, PORTUGAL AND BELGIUM

No major registration issues to report.

EEC

Attempts by Denmark and the Federal Republic of Germany in 1983 and 1984 to have paraquat adopted as a candidate for inclusion in the EEC Prohibitions Directive failed. PSRG is aware that recent attitudes toward soil persistence in Holland and Germany could lead to the matter being re-opened.

OUTSIDE WER

USA

In 1982 paraquat was removed from the RPAR (Rebuttable Presumption Against Registration) candidate list. It was returned to normal registration processes. Registrations are conditional upon the outcome of the newly-available IBT-replacement and allied toxicological data. However, alongside other chemicals, paraquat has become involved in two other processes.

As a result of an out-of-court settlement of a case brought by the National Resources Defence Council (NRDC, an environmental group), EPA agreed to re-review the processes by which 14 chemicals, including paraquat, were removed from the RPAR candidate list. This activity must be completed by 31 March 1986. As part of this activity, EPA has re-evaluated the technical data base on paraquat, including the newly-submitted toxicological data. The review processes are understood to be complete and free of new issues, except under toxicology where review of the new longterm rat study has led EPA to an interim decision that paraquat should be regulated as an oncogen, due to the lung lesions seen in the top dose females. However EPA has noted the difference of opinion between the erstwhile Head of Pathology at the contract lab, LSR, and the Head of Pathology at CTL over the interpretation of the lung lesions. (The CTL interpretation is that the lesions shows no evidence of a compound-induced tumorigenic response). EPA wishes to see this difference resolved before finalising its position in March 1986. To facilitate this, the lung slides are about to go for reading by a third pathologist in the USA.

Early in 1986, the EPA are to issue registration standards for several older pesticides, including paraquat. This means that data previously submitted for registration of these older products must now comply with the EPA's up-to-date standards. Chevron believe this will not present a major problem to us, beyond issues already listed above.

LATIN AMERICA

The wishes of the US Drug Enforcement Agency (DEA) to use paraquat for marijuana eradication has attracted unwelcome attention in the media and elsewhere to some of the properties of paraquat.

In Brazil there have been proposals to limit use in certain States but the constitutionality of these has been contested by the Federal authorities.

Overall there have been no major longterm regulatory decisions against paraquat in Latin America.

JAPAN

Japan has a major problem of suicides. The abuse of paraquat for suicide (and homicide) purposes has drawn attention to the compound. As a result, it is anticipated that during 1986 the 20% liquid paraquat formulation will be replaced by a 4.5% paraquat:4.5% diquat liquid, containing colour, stench and emetic, plus a bittering agent to assist in countering the homicidal abuse (of adultering soft-drinks from vending machines).

MALAYSIA

Considerable media attention has been focused on paraquat, mainly because of its abuse for suicide. Environmental groups are particularly active in Malaysia. However this has not resulted in any regulatory action against paraquat specifically in Malaysia so far.

EASTERN EUROPE

Lines of communication with Holland and Germany have resulted in queries arising (eg in Hungary and East Germany) about soil persistence. So far these have not had any major regulatory consequences.

TK418
GAW/NMW
Jan 86

APPENDIX 2 : SOLID PARAQUAT

1 PROPOSED WORK PROGRAMME

1.1 Objectives

(a) To produce on a six month timescale to mid-1986 a magnesium sulphate 'Weedol'-type granule with the highest possible paraquat ion content consistent with the existing process technology at Yalding to a maximum 20% content. The work should also cover a paraquat-diquat mixed granule.

This programme of work is driven by the need to have a commercialisable 'high' strength granule in place by mid-1986 in case ICI feels the need to submit such a product for registration at that time (eg, in Italy).

(b) To produce on a twelve-month timescale to end-1986 the optimum solid paraquat and paraquat/diquat formulations to a maximum bipyridyl content of 20%. The 'idealised' characteristics of such a granule are attached (Appendix 1).

1.2 Work Programmes

(a) The laboratory and pilot plant work will start end-January 1986 and should be completed by end April. Storage and field trials will follow.

(b) A two-part programme is proposed. Firstly an initial period of 3 months to end-April during which time all the current solid formulation options will be re-assessed and a thorough review of alternative technologies undertaken. This review will cover the new SDS formulation from Japan (details attached in Appendix 2). At the end of this period a lead formulation will be selected for full evaluation (biologically and process-wise) to a commercialisable formulation by end-1986. This evaluation programme will involve possible use of ICI Americas Shugi pilot plant.

(c) Assessment of water soluble packs.

1.3 Resource Needs

(a) 3 man months to end-April, 1986. Yalding redeploying experienced Experimental Officer by end-January.

(b) Product Supply Department/Yalding work group to end-April, 1986. 9 man months thereafter.

(c) Being reviewed.

2 IDEAL CHARACTERISTICS FOR SOLID PARAQUAT FORMULATION

1 20% ion with flexibility in formulation and process so that ion strength can be lowered to say 10%.

2 Dissolves readily in water (viz dissolves in <1 minute in water at 10°C with gentle stirring).

3 Dust free and low friability.

4 Any insoluble residues do not block spray nozzles.

5 Unattractive in appearance - and contain dye, odour, emetic and bittering agent.

6 Form a gelatinous immobile mix at high levels if addition to liquids (similar effect on SDS granule).

7 Biological efficiency of paraquat ion unaffected compared with 'Gramoxone' formulations.

8 Stable on storage eg, non-caking.

APPENDIX 3 : 'THICKENED' 'GRAMOXONE'

1 PROPOSED WORK PROGRAMMES

1.1 Objectives

(a) To develop commercialisable paraquat (100 g ion/l) and paraquat-diquat (100 g ion + 50 g ion) formulations by July 1986 for France.

(b) To evaluate commercialisable paraquat (200 g ion/l) and paraquat-diquat (120 g ion + 80 g ion) formulations by end-1986 for international use. The thickened/greened formulation could provide a most effective visual alerting agent to supersede the current blueing if appropriate. The 'idealised' characteristic of such a granule is attached (Appendix 3).

1.2 Work Programmes

(a) The Sopra factory at Bernay will continue to lead this development. Yalding input is restricted to:-

- Storage stability checks up to 50°C for 6 months
- Effect of low temperatures (near zero) on viscosity and dilution properties
- Check batch-to-batch variation in quality of paraquat concentrate particularly for cationic wetter and iron salts content - BC to action
- Check other routes to paraquat, eg cyanide route
- Optimise viscosity/dilution properties with ongoing effort to monitor storage samples over a 6 month period.

This work will take 2-3 months with ongoing effort to monitor storage samples over a 6 month period.

(b) The following outline programme is envisaged over 9-12 months:-

- Optimise viscosity/dilution properties by use of various wetting agents, silicons and polymers
- Check effect of low temperatures and high temperatures on viscosity and dilution properties
- Check effect of paraquat quality and different routes
- Check storage stability up to 50°C.

1.3 Resource Needs

In total 1 man year at Yalding.

2 TARGET SPECIFICATION FOR THICKENED 'GRAMOXONE'

2.1 Appearance

Unattractive, coloured, viscous liquid continuing stench, emetic and bittering agents.

2.2 Active Strength

20% paraquat ion or 10% paraquat ion and 10% diquat ion.

2.3 Viscosity

7 to 10 times that of standard 'Gramoxone'.

2.4 Dilution

Not more than 30 seconds in a range of water hardeners.

2.5 Suspensibility

Not more than 0.02% w/w of 5 g product dissolved in 500 ml water should be retained on a 100 mesh sieve.

2.6 Pourability

Good flow and drainage from sales pack but difficult to pour into another bottle.

2.7 Storage

Stable for 2 years at least at 25°C. Viscosity not seriously reduced at higher temperatures. Recovers from freezing.

2.8 Foaming

No worse than standard 'Gramoxone'.

APPENDIX 4

19-17

From
G A Willis
Head
Product Safety and Registration

ICI PLANT PROTECTION DIVISION
Fernhurst
Haslemere Surrey GU27 3JE

Telephone Haslemere (0428) 4061
Direct Line Redacted - EU PII
Telex 858270 & 858512 Icipp Fernhurst

To
Dr A K Stapleton
Herbicides Product Manager

Copies to Dr D H Brooks
Mr J C Francis
Mr T C Frears
Mr D F Manning
Mr R A Woods
Mr C S Major
Mr P Bramley
Dr G M Farrell
Dr T B Hart
Dr L L Smith
Mr N G E Geach
Mr A G Potter
Dr P Slade

CONFIDENTIAL

Your ref	Our ref	Tel ext	Date
	GAW/NMW	Redacted - EU PII	23 JAN 86

REPORT OF PSAC SUB-COMMITTEE ON EMETIC INCLUSION RATES

The sub-committee constituted by the 1 November 1985 PSAC has met several times since then. Membership has been drawn from Peter Bramley, Nick Geach, Bernard Hart, Alan Potter, Peter Slade, Lewis Smith and myself. On 1 November the PSAC agreed that the effect upon human fatality statistics of increasing the PP796 content of paraquat formulations should be studied. The sub-committee was formed to take the matter forward and you received a verbal progress report at the last PSAC.

Because of what we already know about the pattern of poisoning incidents and their outcome, the sub-committee has agreed that, in the first instance, it would be worthwhile only to study situations where formulations containing about 5-12% paraquat are sold. (The mortality rate of only about 10% seen with 2.5% formulations would make it difficult to measure any effect of adding extra PP796 while there is evidence from the existing incidents where large doses of the 20% product are taken to predict that a 5-fold increase in emetic dose will not result in a measurable decrease in % mortality).

To make a study worthwhile, the sub-committee concluded that the following criteria would also need to be met:

1. Sufficiently high incident rate to yield information over a period of a few years at the most.

2. Ability to monitor fatal and non-fatal incidents adequately.

3. Adequate product identification and an ability to bring a revised product into the trade widely over a short time span.

4. Regulatory procedures would be such that such a study could be conducted.

After considerable debate, the sub-committee has concluded that it would be appropriate to study the inclusion of 40 mg PP796 in a minimum lethal dose of product, for products in the paraquat concentration range up to 12%. (The sub-committee has not agreed a figure for inclusion in 20% products since we are not recommending that these be the subject of study at present - see above.) The inclusion of 40 mg in the minimum lethal dose of a 5% paraquat product of about 40 ml would lead to an emetic inclusion concentration in that formulation of 0.1%. For a 10% formulation the emetic inclusion concentration would be 0.2%.

The sub-committee has considered (or has taken specialist advice on):-

a) whether such concentrations are capable of being achieved in formulations in practice

b) whether they would have any adverse effect upon the treatment of poisoning (ie by causing violently excessive vomiting

c) whether they are likely to have any effect on the normal user, and

d) whether they would be acceptable environmentally.

At the concentrations mentioned above, none of these four points is considered to be a problem.

Although paraquat:residual cols containing circa 10% paraquat are sold quite widely, the incident rates with them are generally low. Thus, on the basis of the information available to the sub-committee, they fail to meet criterion No. 1 above and so do not provide a worthwhile opportunity for studying the effects of increased emetic concentration.

The new 4.5% paraquat/4.5% diquat PREEGLOX L formulation due to enter the Japanese market later this year, would in principle provide an opportunity of a study which would meet the sub-committee's criteria. However to do so we would need to be sure that

i) the emetic inclusion rate would meet the sub-committee's criteria - ie it would need to be included at 0.1%

ii) adequate monitoring is possible.

Regarding (i), the sub-committee is cognisant of concerns over emetic inclusion rates which have been expressed by some doctors in Japan. However it believes that these concerns are misplaced for a 0.1% inclusion rate in the proposed PREEGLOX formulation. Drs Hart and Smith have been charged with producing a supporting document on this point, for despatch to ICI Japan by the end of February. The sub-committee anticipates that they will need to follow-up with a joint visit to discuss the points which it makes, in say March/April.

Regarding (ii), monitoring on a limited geographical basis in Japan is likely to prove more useful than attempting to cover the whole of Japan less well. During their proposed visit Drs Hart and Smith would need to look further into this. Dr Hart is charged with initiating the process of evaluating such possible areas.

Because of various uncertainties surrounding Japan, the sub-committee deems it wise to have at least one, and preferably two, back-up options for such studies.

The change in France to a thickened 10% paraquat/5% diquat formulation containing 0.2-0.25% PP796 would in principle provide an opportunity of a study which would meet the sub-committee's criteria. There would be a need of greater monitoring resource in the Paris Antipoisons Centre and in Ile de la Reunion and the French Antilles. There is an action on Alan Potter, Bernard Hart and myself to continue to follow-up with ICI SOPRA. Of course the results could be confounded by a product name change and/or a switch to the thickened formulation. Nevertheless if the combination of measures was shown to be of major benefit, there might not be any pressing need to try separating the contributions of the individual components to the whole benefit. The new formulation is expected to be in the market place during 1988 but it could require several years for sufficient information to be forthcoming to facilitate an assessment of the benefits.

Because of the uncertainties surrounding Japan and the potential effects of the confounding factors mentioned above in the French option, the sub-committee has not yet identified a viable and reliable opportunity of studying the effect of the increased emetic concentration in isolation in situations which meet our study criteria. We would be interested to receive suggestions (informally) of situations in which a study could be initiated. We propose to think further about possible situations in the meanwhile.

The sub-committee will continue to meet regularly to keep the subject under review. The sub-committee also takes the view that it would be an appropriate body to undertake detailed consideration of allied topics for the PSAC and proposes that its terms of reference should be expanded accordingly. Those topics would include ones specifically assigned to it by the PSAC and ones which it could usefully tackle on its own initiative.

pp G A WILLIS

COMPANY SECRET

This document has been circulated by

PSAC

PARAQUAT STRATEGIC ACTION COMMITTEE

MEMBERS

A K Stapleton (Chairman)
D H Brooks (Deputy Chairman)
G M Farrell
C S Major
T B Hart
G A Willis
D F Manning
R A Woods
T C Frears
J C Francis
L L Smith
P J Bramley (Secretary)

COPIED TO:

C A Spinks
A G Potter
G Villani
R D Morrison
W C Stonebridge
M J J Bennett
J J Batch
M J Northcott
R A Morrison
N G E Geach
W D McClellan
M S Thomas
W R T Cottrell
A J Robinson

MINUTES OF THE FIFTH MEETING OF THE PARAQUAT STRATEGIC ACTION COMMITTEE
HELD ON 2 DECEMBER 1986 AT FERNHURST

Present : A K Stapleton (Chairman)
J C Francis
A G Potter
A J Robinson
R D Morrison
R A Morrison
T B Hart
L L Smith
C S Major
G M Farrell
P J Bramley (Secretary)

1. Evaluation/development of compounds alternative to paraquat and/or diquat in the event of loss of registrations

WER gave a short presentation describing the evaluation work they are doing with alternative compounds for:-

(a) paraquat

in potatoes - PP005/metribuzin (oil)
in vines - PP005/diquat, MCPA (oil)
- diquat/glyphosate
- PP005/fomesafen
- glyphosate?

Increasingly in Northern Europe 'Basta' (glufosinate) is now the accepted norm and provides a lower control level than that previously provided by paraquat.

(b) diquat

These registrations are now also under pressure in WER (especially Denmark, Holland and West Germany).

WER would like to be able to offer through PSR low strength diquat mixtures as "compromise" solutions to registration authorities, if necessary, in an attempt to retain these registrations (total WER GGM of £m could be under threat). A diquat and metoxuron mixture is favoured for Holland. It was agreed that on a global basis to lose a diquat registration totally is the worst scenario. The pressure on dinoseb in Holland (it is a very significant desiccant in that market) is working in ICI's favour.

ACTION : RDM to confirm that offer of diquat and metoxuron is acceptable to EMA Region in the above extreme circumstances.
Paraquat Mixtures Work Group to consider other alternative back-up products.

The evaluation programme was supported but it was agreed that before WER (or any other Region) move into development proper, involving registration authorities and/or outside bodies, the prior support of PSAC would be obtained.

Note: Paraquat Research Work Group is currently re-evaluating the alternative bipyridyl compounds in the light of both their toxicity and soil residue properties. Inevitably such a solution could only come to fruition in the medium term.

2. Publicity on the benefits of paraquat to world agriculture

With various governments now taking steps to limit agricultural production (eg, EEC) it is clear that it is more likely ag chemical registrations will be lost without the agricultural benefits case winning the day, as has been the case in Scandinavia. The need for ICI to revamp its efforts in this area was reconfirmed.

Reporting on actions following the last meeting CSM described 5 possible areas of work:
(a) reference book
(b) film or video (Cost £60,000 for 30 minutes)
(c) Prestige leaflet/brochure along the lines of the "Pyrethroid Story" (Cost £6-8000)
(d) Speakers' pack with slides etc but flexible (Cost £5000)
(e) "Seeding" learned articles in the press etc.
It was agreed that is was essential to be clear who is the target audience before a final decision is made. Areas (c) and (d) were preferred by the meeting.

ACTION : The Product Stewardship Work Group will consider these proposals in detail as a matter of priority (P Slade/PJB).

3. Latest Registration Position

The most recent PSR update on this issue is attached. In addition the following comments were made on the US position:-

(a) Paraquat

Paraquat - USA Registration

Following the EPA's release of the draft registration standard on paraquat, ICI's comments through Chevron have now been submitted. We are not aware of any other organisation having provided comments to the EPA. There will be an inevitable delay of several months, before the EPA issue a final standard, which should encorporate our comments.

A major issue to be resolved, however, is the EPA's review of the rat life-time study. Although the lung issue has subsided for the time being, the EPA have classified paraquat as a Class C oncogen based on effects on the head and neck. These effects were squamous cell carcinomous, but their site of origin (nasal mucosa or skin) is unknown. If paraquat remains as a Class C oncogen, it could well prevent registration of new outlets involving food crop residues.

Diquat - USA Registration

A registration standard for diquat was also issued in August 1986, but unlike the paraquat standard is as a final version and not a draft. Different EPA product managers and the relative paucity of data on diquat compared with paraquat may account for the different statuses of the standards.

The standard involved proposals for many studies, principally those involving environmental fate, as well as proposals for reclassification, user restriction and label changes. Chevron and ICI jointly met with the EPA to clarify these issues in September and as a result of that meeting, several proposals, including those on user restriction, label changes and reclassification seem to be no longer applicable.

ICI and Chevron will maintain a close liaison to plan, monitor and report the studies on diquat required by the standard.

PJB/TBH
13.02.87

PARAQUAT REGISTRATION - MAJOR ISSUES

FAR EAST AND PACIFIC

JAPAN

Japan has a major problem of suicides. The abuse of paraquat for suicide (and homicide) purposes drew attention to the compound. As a result during 1986 the 20% liquid paraquat formulation was replaced by a 4.5% paraquat:4.5% diquat liquid, containing colour, stench and emetic, plus a bittering agent to assist in countering the homicidal abuse (of adultering soft-drinks from vending machines). A name change to PREEGLOX L has also being used as a means of trying to divert the attention of potential suicides away from paraquat, previously sold as GRAMOXON, although the extent of future media attention to paraquat may limit the usefulness of this move.

Prof Naito has been advocating the development of a solid formulation which forms a paste upon initial dilution with water. This would be as a measure to try to limit potential suicides (NB. The paste could still be taken deliberately). Development work continues, although the future of the project remains uncertain.

MALAYSIA

Considerable media attention has been focused on paraquat, mainly because of its abuse for suicide. Environmental groups are particularly active in Malaysia. Under new schemes for licensing dealers and users proposed earlier this year, paraquat would have been classified as a highly toxic pesticide. Users would have been required to undergo three-monthly medical checks and sprayed areas would have needed to be signposted. Neither of these provisions is necessary in the case of paraquat. ICI and the trade association objected. As a result, the government has not progressed with the proposals. Dialogue continues.

Ministry of Health concerns surrounding paraquat toxicity and mis-use will continue to have a de-stabilising influence on the registration situation.

WESTERN EUROPE

FRANCE

In October 1982, the Commission des Toxiques (regulatory committee) recommended that liquid formulations of paraquat should be limited to a maximum strength of 4%. [NB. A 4% liquid product had been on sale already to smallholders and the 20% into main agricultural and horticultural outlets.] The Commission's recommendation came about because of concerns over poisoning incidents, mainly in the French Antilles. The recommendation required the endorsement of several ministries, including the Ministry of Agriculture, before a regulation could be issued. The Ministry of Agriculture has refused to countersign the proposal so far, on grounds of its present impracticability. Thus GRAMOXONE 2000 has remained on sale. However, in principle (but see below), any new paraquat registrations, whether of ICI or non-ICI products, would have to comply with the 4% proposal. The inclusion of colour, stench and emetic are mandatory.

As a further safening proposal, ICI SOPRA have introduced the French authorities to the concept of a thickened formulation. The SOPRA proposal was to thicken the 20% formulation but initial indications are that the authorities will seek a concurrent reduction in paraquat content to 10% (but not down to 4%). Trials using thickened formulations (one containing 10% paraquat:5% diquat) are scheduled during 1986, with a view to product entering the market during 1987/8.

FEDERAL REPUBLIC OF GERMANY

Registrations in the Federal Republic run for a maximum of ten years, after which they have to be renewed if sales are to continue. The registrations for GRAMOXONE, GRAMOXONE S and DUANTI (equals WEEDOL) expired at the end of 1983. The authorities have refused to re-register them. The Federal Health Authority (BGA) gave its consent to continued registration of products containing up to 10% paraquat. However the regulatory agency (BBA) refused to renew registrations "because of the behaviour of paraquat in soil".

At the centre of the dispute between ICI and the authority is the unwillingness of the authority to accept the evidence for the degradation of paraquat in soil in the field. The authority argues that use at the maximum permitted rate for the duration of registrations hitherto has the potential, in extreme cases and in the absence of any degradation, to saturate the deactivation capacity of soils, leading to a potential for residual phytotoxicity, "an imminent hazard" which the authority considers it needs to legislate for. In this process, the authority argues that it cannot differentiate between soil types.

The ICI position is that paraquat residues decline in soil in the field, albeit slowly but nevertheless at a rate which will be sufficient to ensure that an equilibrium is reached between annual addition rate and annual degradation of the paraquat present, before the deactivation capacity is saturated in the overwhelming majority of agricultural and horticultural soils. In extreme cases of peats and of sands of less than 5% clay content, amendments to use patterns, where required, would in practice obviate any possibility of the deactivation capacity being exceeded. No practical example has come to ICI's attention where the normal uses of paraquat have led to the deactivation capacity being exceeded and of consequent residual phytotoxicity.

ICI's objections to BBA about their decision were rejected. Therefore ICI had no option but to take the matter to the Administrative Law Court, which heard the case on 21 February. In principle, the Court found in favour of ICI and that the BBA action was incorrect. The Court set the question whether or not soil SACs could ever be exceeded and, if so, in what circumstances. The Court urged the two parties to seek an out of court settlement. Failing that, they should agree to a technical expert being brought in to arbitrate. Despite ICI's continued willingness to compromise, no out of court settlement looks likely. Meanwhile a court ruling is expected by the end of 1986 in favour of restoring registrations on some soil types. If this happens, BBA may appeal and thus cause further delays.

Meanwhile registrations of various paraquat:residual mixtures, containing up to 10% paraquat, remain in place. They are scheduled to run until 1990.

THE NETHERLANDS

In 1985 The Netherlands finalised a policy document which decreed that pesticides which are persistent in soil are fundamentally undesirable. This is irrespective of whether or not that persistence is of any phytotoxicological or other ecotoxicological consequence. The availability of (perceived) alternatives needed also to be considered when deciding on the registration/ re-registration of such compounds.

On this basis, the pesticide registration committee (CTB) has formulated a recommendation to the Deputy Minister of Agriculture that registrations of paraquat- and diquat-containing products should not be renewed when they expire in November 1988.

Despite good technical-level meetings and an ICI offer of labelling restrictions to ensure no possibility of the soil deactivation capacity being exceeded even in extreme situations, the committee has stuck to its position. ICI has appealed and has enlisted the support of the influential Landbouwschrap (National Farmers' Union equivalent). The case continues.

In 1983 ICI Holland agreed that various municipal uses of GRAMOXONE should be switched to WEEDOL to minimise any possible consequences of humans and pets gaining improper access to the undiluted 20% liquid during use by municipalities.

SWITZERLAND

At the authorities' request, ICI/Maag submitted in April 1985 the standard review of paraquat residues in soil.

In December Maag learned that the Swiss authorities were planning to discontinue all uses of paraquat and diquat because of concerns over soil persistence. A meeting therefore took place between ICI/Maag and the authorities on 7 January.

Although the authorities have reached this view, they have not yet initiated the process which would be needed to give effect to their view. At the 7 January meeting, ICI agreed to make a further submission in February on points of technical detail which arose during the discussion. On the basis of the information provided by Maag, ICI has not identified any use situations which would merit introducing a limitation on use. Nevertheless ICI indicated that it would be prepared to conduct a survey (c/f other WER countries) of residues in any situations which are of particular concern to the authorities and, if the results indicated a need, to volunteer use limitations to preclude the longer-term possibility of residual phytotoxicity. Maag/ICI await a Swiss reaction. The Swiss activities have been influenced by events in The Netherlands and Germany and thus any failure to maintain registrations in either of those two countries could have a "knock-on" effect on Switzerland.

In Switzerland, the authorities decided in April 1985 that the paraquat content of registered products should be limited to 12%, effective from August 1986. This move was initiated in the face of pressure concerning the toxicity of paraquat and its abuse for suicides. Maag has switched emphasis to an existing alternative paraquat and diquat-containing product and has dropped use of the trade name GRAMOXONE. The word paraquat has disappeared from the label and instead the systematic chemical name is being used. These moves are intended to reduce the identification hitherto with the product amongst those who are

considering the act of suicide. The classification system in Switzerland limits the availability of such products, including GRAMOXONE, to bona fide agriculturalists and horticulturalists.

SCANDINAVIA

Denmark introduced a proposal five years ago to re-register all existing products before 1 January 1986. Those which had not been registered under this new scheme by that date would cease to be registered on that date. In April 1983 the Danish regulatory body gave ICI Denmark notice that GRAMOXONE and PRIGLONE (equals WEEDOL) would not be re-registered. The regulatory body said that its decision was made mainly because of concerns over toxicity and safety in use. A concurrent and similar decision on diquat was made on environmental grounds. A perceived lack of need of paraquat, and the existence of perceived alternatives, influenced the decisions.

ICI Denmark objected. In December 1984 the Appeals Board instructed the regulatory body to reconsider its decision, which it has not yet done. Meanwhile the re-registration process was abandoned in November 1985 and all existing registrations continue without time limit. However new rules are being formulated which are likely to put paraquat registrations in Denmark in jeopardy in the longer term.

In view of official concerns over the toxicity of paraquat, ICI voluntarily withdrew GRAMOXONE registrations in Sweden, effective 31 December 1983, in the understanding that a solid formulation (c/f WEEDOL) would be registered in its place (NB. By many European standards, the Swedish uses would have been classified as smallholder.) In the event, the authority refused to register any new formulation of paraquat, on the grounds of inherent toxicity and lack of need, ie perceived alternatives. There is no effective appeals procedure in Sweden.

In Finland, the Pesticide Board, mainly on advice from the Board of Health (Ministry of Health) have cancelled the acceptance and import of GRAMOXONE in Finland. Registration expired in August 1986. The Pesticide Board's decision is based on the 'toxicity of paraquat', although there have only been 2 suicide deaths in Finland in 20 years and no fatal accidents or problems with use of the chemical. ICI's appeal against this decision, through the distributor, Berner Osakeyhtio, was denied.

Registrations in Norway are due to expire and re-registration has been applied for, with no reaction at this very early stage.

ITALY

The authorities called in an up-to-date submission on the compound in 1985. The re-evaluation was completed during the first four months of 1986. As a result, ICI Solplant were required to include colour and stench in GRAMOXONE and SECCO TUTTO, and to introduce improved caps on certain containers. Certain very minor uses have disappeared from the paraquat labels in favour of the use of other compounds such as diquat. Initial Italian proposals to require a solid or dilution have been dropped. A survey of soil residues versus SAC is a requirement of continued registrations.

SPAIN

The Authority has decided to conform to EEC registration standards. They have decided that because paraquat is in the most poisonous class in most EEC countries, it should similarly conform in Spain. However, the fourth class category in Spain will restrict application to approved contractors and place an unreasonable limitation on sale. A dossier has been submitted to obtain a fuller review by the Spanish authorities and the outcome is awaited.

UK

No major registration issues on paraquat to report.

EEC

Attempts by Denmark and the Federal Republic of Germany in 1983 and 1984 to have paraquat adopted as a candidate for inclusion in the EEC Prohibitions Directive failed. PSRG is aware that attitudes toward paraquat in Holland, Denmark and Germany could lead to the matter being re-opened.

AMERICAS

USA

In 1982 paraquat was removed from the RPAR (Rebuttable Presumption Against Registration) candidate list. It was returned to normal registration processes. Registrations are conditional upon the present review of the newly-available IBT-replacement and allied toxicological data. However, alongside other chemicals, paraquat has become involved in two other processes.

As a result of an out-of-court settlement of a case brought by the National Resources Defence Council (NRDC, an environmental group), EPA agreed to re-review the processes by which 14 chemicals, including paraquat, were removed from the RPAR candidate list. As part of this activity, EPA re-evaluated the technical data base on paraquat, including the newly-submitted toxicological data. The review processes are complete and free of major new issues, except under toxicology where review of the new longterm rat study has led EPA to an interim decision that paraquat should be regulated as an oncogen. The debate with EPA is likely to continue into 1984.

The draft registration standard arising from the reviews requires further residues and environmental studies.

LATIN AMERICA

The wishes of the US Drug Enforcement Agency (DEA) to use paraquat for marijuana eradication has attracted unwelcome attention in the media and elsewhere to some of the properties of paraquat.

In Brazil there have been proposals to limit use in certain States but the constitutionality of these has been contested by the Federal authorities.

Overall there have been no major longterm regulatory decisions against paraquat in Latin America.

EASTERN EUROPE

Lines of communication with Holland and Germany have resulted in queries arising (eg in Hungary and East Germany) about soil persistence. So far these have not had any major regulatory consequences.

TABLE OF MAJOR PARAQUAT REGISTRATION ISSUES (3 NOV 1986)

Country	Remark
France	Proposal to reduce 'GRAMOXONE' to 4% has not been implemented. New thickened formulations containing 10% paraquat under development for 1987/8 introduction. Colour, stench and emetic mandatory.
Germany	'Gramoxone' and other products denied re-registration at end of 1983 on grounds of soil persistence. 2/86 court hearing found in favour of ICI in principle. ICI offers of amended use patterns to preclude SAC being exceeded in extremis have not been taken up. Meanwhile a court judgement is expected by end 86 in favour of restoring registrations on some soil types. [NB. BBA could always appeal, causing delay.]
Holland	Because of philosophical concerns on soil persistence, authorities propose paraquat and diquat registrations should not be renewed when they lapse 11/88. ICI appealing and has offered amended use patterns (c/f Germany).
Hungary	Quiet at present. Risk of official concern re toxicology and soil persistence arising again during 1987.
Italy	'Gramoxone' and 'Secco Tutto' re-registered Spring 1986. Colour, stench and emetic mandatory. Soil survey required.
Japan	'PREEGLOX' [4.5/4.5 pq/dq] has been introduced. Contains colour, stench and emetic, plus bittering agent to counteract homicide abuse.
Latin America	Continued tox concerns in public domain, fanned by marijuana affair, have not yet resulted in major longterm regulatory decisions against paraquat. In Brazil, proposals to limit use in certain States are being contested by Federal Authorities.
Malaysia	Possible use restrictions, requirements for regular health checks and signposting sprayed areas proposed earlier in 86 have not been adopted. Dialogue with authorities continues.

/.....

Continued/2

Country	Remark
Scandinavia	Paraquat-containing products remain on market in Denmark despite earlier authority attempt not to re-register. No longer registered in Sweden and Finland.
Spain	Use classification (affecting availability) is under review since Spain joined EEC.
Switzerland	Concerns re soil persistence fuelled by Germany and Holland. Maag/ICI still talking with authorities. Survey of paraquat residues in soil offered. Possible longer-term offer of use limitations (c/f Germany). PREEGLONE (12% paraquat:8% diquat) have been introduced to replace GRAMOXONE to try to counter suicide issue (as required by officials).
UK/Ireland	(Quiet.)
USA	Draft registration standard requires further residue and environmental studies. Assessment of tumorigenic potential during chronic feeding to rats not now likely to be completed until 1987.
EEC	(Quiet).
JMPR/CCPR	Paraquat tox was favourably re-evaluated by 1986 JMPR meeting. Full ADI set Report due end 86.

C2.1/05

Category B Report (Confidential)
Not to be copied except by a Reports Centre

Copy No: 17

T.P. 554/76

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

Revised 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, 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 (Case and Dunlop, 1977). 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 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 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 2 mg. 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 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).

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.

TABLE 1

The emetic action of PP 796

	Dose	Nos. Vomiting	% Vomiting response	Total dose (mg)
Dog*	0.5 mg/kg	3/8	35	
	1.5 mg/kg	6/8	75	
Pig**	0.25 mg/kg	0/8	0	
	0.5 mg/kg	3/8	35	
	1.0 mg/kg	5/8	63	
Monkey &** Marmoset	0.05 mg/kg	0/5	0	
	0.1 mg/kg	5/24	21	
	0.2 mg/kg	8/19	42	
	0.3 mg/kg	2/15	13	
	0.4 mg/kg	5/15	33	
	0.5 mg/kg	4/5	80	
	1.0 mg/kg	2/2	100	
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 Todd (1977)

\+ Data from Bayliss (1973)

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

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

IMPERIAL CHEMICAL INDUSTRIES PLC
PHARMACEUTICALS DIVISION

TITLE :- A summary of clinical results of the phosphodiesterase inhibitor ICI 63,197 in a variety of disease states

AUTHOR(S) :- Bayliss P F C

DATE :- 23 July 1971

PH20992BC

IMPERIAL CHEMICAL INDUSTRIES LIMITED

PHARMACEUTICALS DIVISION

Title: A Summary of Clinical Results of the Phosphodiesterase Inhibitor ICI 63,197 in a Variety of Disease States.

Author: P.F.C. Bayliss

Submitted by: P.F.C. Bayliss

Copies made: 24

Issuing Dept.: Clinical Research

Date: 23rd July, 1973.

A SUMMARY OF CLINICAL RESULTS OF THE PHOSPHODIESTERASE INHIBITOR ICI 63,197 IN A VARIETY OF DISEASE STATES

P.F.C. Bayliss,
Clinical Research Department,
Imperial Chemical Industries Ltd.,
Pharmaceuticals Division,
Mereside,
Alderley Park,
Macclesfield,
Cheshire.

I N D E X

INTRODUCTION

ICI 63,197 was initially selected to go to clinical trial upon the basis of its anti-bronchoconstrictor effect in animals. Further work revealed that it had a variety of effects in animals suggestive of a possible central nervous system action. Clinical trials were begun in a variety of disease states in addition to studies in normal volunteers. At an early stage it became obvious that the agent had a variety of unpleasant side effects (nausea, vomiting, dizziness, flushing) at low doses (1 - 4 mg.) which made clinical trials difficult to conduct. At a later stage the agent appeared to induce angina pectoris in two patients with no previous history of the complaint. Because of this, and the fact that no beneficial effect had been seen in pilot studies, it was decided that no further work should be done with the agent and that existing trials with the agent should be wound up.

This report summarises the results seen in various areas of medicine. The appendix contains a brief description of each trial carried out, together with what results we possess. It will be appreciated that because of the severe side effects, lack of beneficial effect and difficulty in predicting a target disease state in which ICI 63,197 might be effective it was only possible to study small numbers of patients, most trials being stopped or abandoned rather than reaching completion.

SUMMARY OF RESULTS

1. Respiratory system

No evidence of protection against histamine induced bronchospasm (aerosol or i/v histamine) could be shown. No potentiation of the broncho-dilator effects of isoprenaline or salbutamol were shown.

2. Cardiovascular system

No consistent effect was seen upon the blood pressure of either normotensive or hypertensive subjects. No consistent effect on pulse rate was seen. No evidence of potentiation of the effects of isoprenaline on heart rate were shown. Angina pectoris seems to have been induced in 2 subjects.

3. Psychiatric disorders

No beneficial effect was seen in patients with anxiety, depression or schizophrenia. In depression there was a suggestion that there was a worsening of the depressed mood.

4. The endocrine system

ICI 63,197 did not produce any effect in thyroid or adreno-cortical function. In one female subject there was a surge in LH levels. No consistent effect was produced upon a standard intravenous glucose tolerance test. There was a suggestion that ICI 63,197 suppressed the rise in insulin levels following an oral glucose load.

5. Obesity

No effect on body weight was shown.

6. Pharmacokinetics

The halflife of ICI 63,197 was between 1½ and 3½ hours.

7. Side effects

Nausea, vomiting and dizziness were commonly seen with ICI 63,197 at 1 mg. unit doses and above. Angina pectoris appeared on chronic dosing of 2 mg. TDS in 2 patients after 4 and 6 weeks respectively. Capillary fragility with a positive Hess's test was seen in one subject.

APPENDIX

Summaries of all clinical trials

CLINICAL PHARMACOLOGICAL STUDY OF ICI 63,197 IN NORMAL VOLUNTEERS

(PROFESSOR J. CROOKS, DUNDEE)

PROTOCOL

Fit, healthy University students were selected for the study. Informed consent was obtained from each volunteer. Subjects were not on any other medication at the time of the test.

Each subject took on one occasion a dose of ICI 63,197 of between 0.25 and 8 mg., when the following parameters were measured:-

a) Blood level of ICI 63,197 at 1, 2, 3, 4, 5, 6, and 8 hours after the dose.

b) Pulse rate and blood pressure at -10 minutes, 0 and 1, 2, 3, 4, 5, 6, and 8 hours and 3 days after the dose.

c) Plasma L.H., P.B.I. and cortisol at -10 minutes and 1 hour after a dose.

d) A blood sample was taken at -10 minutes and 4 hours and 3 days after the dose for Hb, WBC, diff. ESR, alkaline phosphatase, bilirubin, SGOT, 5 NT, urea, sodium, potassium chloride, albumin and globulin.

e) A urine sample was tested at -10 minutes and 4 hours after the dose for protein (albustix) and sugar (clinistix).

f) Two 24 hour urine collections, one immediately before and one immediately after dosing.

A note was made of any adverse effects encountered.

RESULTS

Details 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 1½ - 3½ hours in this series.

Effect on pulse rate and blood pressure

Pulse rate (beats/min.)

		Time (hrs.)								
No.	Dose(mg.)	-10 mins	0	1	2	3	4	6	8	3 days
1	0.25	95	80	80	80	80	80	80	80	80
2	0.5	90	90	88	68	80	80	80	80	80
3	1.0	75	75	90	72	80	80	80	80	72
4	1.0	92	84	80	80	84	80	80	80	80
5	2.0	90	96	98	96	96	96	94	96	90
6	2.0	92	84	82	76	80	80	82	80	80
7	2.0	90	88	84	88	84	80	80	88	84
8	3.0	88	72	56	56	-	64	72	72	72
9	3.0	80	76	68	68	-	84	76	80	72
10	4.0	76	78	76	78	78	78	60	60	66
11	4.0	88	84	74	66	68	66	66	60	66
12	8.0	72	86	66	68	66	68	60	64	66

Blood pressure (mmHg.)

		Time (hrs.)								
No.	Dose(mg.)	-10 mins	0	1	2	3	4	6	8	3 days
1	0.25	120/70	120/70	110/70	110/60	100/60	100/60	110/60	110/60	100/60
2	0.5	130/70	130/70	130/70	110/70	110/60	110/60	100/60	90/60	110/70
3	1.0	110/70	110/70	110/70	100/70	100/60	100/60	100/60	100/60	110/75
4	1.0	110/70	-	120/70	100/70	100/60	110/60	110/60	120/70	110/60
5	2.0	110/70	100/60	100/60	110/60	90/60	100/60	100/60	100/60	110/70
6	2.0	110/60	-	110/60	110/60	100/60	110/60	110/70	110/70	110/65
7	2.0	140/80	130/75	105/75	110/80	110/70	120/80	120/80	120/80	140/80
8	3.0	100/70	120/70	105/70	100/70	100/70	105/70	115/75	100/60	110/70
9	3.0	140/80	120/70	100/70	110/80	115/80	110/70	120/70	130/80	140/80
10	4.0	110/60	100/60	100/60	90/60	80/50	100/60	100/80	100/60	110/60
11	4.0	140/70	-	110/70	110/70	100/50	115/80	170/70	120/70	130/70
12	8.0	150/60	150/60	100/60	120/80	120/80	120/80	120/80	130/80	150/80

Effect on plasma, L.H., protein bound iodine and cortisol

L.H. levels (m.IU/ml.)

			Time (mins.)						
No.	Dose(mg.)	Sex	-10	10	15	30	60	120	150
1	0.25	F	9.0				41.0	8.0	
2	0.5	M	11.0				8.1	5.0	
3	1.0	M	8.3				5.2	8.0	
4	1.0	M	13.0					4.7	
7	2.0	F		47.0		20.0	17.0		12.5
8	3.0	M		16.5	10.0	18.0	23.0	11.5	
9	3.0	M		16.0	10.0		33.0		17.5

Protein bound iodine

		Time (mins.)	
No.	Dose(mg.)	-10	60
1	0.25	7.4	6.9
2	0.5	5.9	6.0
3	1.0	7.4	7.0
4	1.0	4.9	5.2
5	2.0	9.4	9.3
6	2.0	5.1	5.2
7	2.0	4.2	3.7
8	3.0	4.0	5.0
9	3.0	6.2	5.8
10	4.0	5.4	5.7
11	4.0	5.5	5.4
12	8.0	5.4	5.4

Cortisol level

		Time (mins.)	
No.	Dose(mg.)	-10	60
1	0.25	17.1	12.0
2	0.5	23.8	10.9
3	1.0	16.0	17.6
4	1.0	20.2	11.2
5	2.0	26.3	29.8
6	2.0	18.9	11.7
7	2.0	22.9	26.9
8	3.0	28.0	22.7
9	3.0	13.4	12.9
10	4.0	23.8	34.3
11	4.0	17.0	17.0
12	8.0	26.8	25.8

Effect on 24 hour cyclic Amp levels (μ moles/24 hours)

No.	Dose(mg.)	24 hrs. before dose	24 hrs. after dose
1	0.25	3.71	4.33
2	0.5	2.69	3.95
3	1.0	4.35	4.9
4	1.0	3.13	2.71
5	2.0	2.26	-
6	2.0	2.37	-
7	2.0	3.18	1.68
8	3.0	5.36	3.44
9	3.0	4.96	2.88
10	4.0	3.79	5.25
11	4.0	5.15	1.19
12	8.0	1.4	4.21

Blood tests

Hb, WBC, diff.ESR, alkaline phosphatase, bilirubin, SGOT, 5 NT, urea, sodium, potassium, chloride, albumin and globulin levels at 4 hours and 3 days did not differ significantly from the pre-dose figures.

Urine tests

Neither protein nor sugar were detected in the urine at 4 hours or 3 days.

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 ¾ - 2 hours.
9	3.0	At 30 minutes dizzy, pale, sweating. Nausea marked.
10	4.0	Nausea and flushing at 15 minutes. Vomited at 30 minutes. Light headedness for 2 - 3 hours.
11	4.0	Dizziness, flushing of face, sweating from ½ - 2 hours.
12	8.0	At 30 minutes sweaty, flushed and light headed. Vomited at 2 hours.

CONCLUSIONS

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

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

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

(3) One female subject (on the lowest dose) showed a surge of L.H. at 1 hour that was back to normal by 2 hours. No effect was seen on P.B.I. No regular effect was seen on cortisol levels although in some subjects there was a fall at 1 hour.

(4) The 24 hour urinary excretion of cyclic AMP rose in subjects after ICI 63,197, although in others it fell.

(5) The agent was poorly tolerated at doses above 1 - 2 mg. Nausea, vomiting, dizziness, sweating and flushing were complained of.

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 ½, 1, 1½, 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 ½ and 1 hours, a light meal between 1½ and 2 hours and a cup of tea between 4 and 5 hours.

RESULTS

Details 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 (µg/ml)

	Time (hrs.)					
No.	½	1	1½	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 µg/ml.

Effect on Human Growth hormone

	Time (hrs.)								
No.	0	½	1	1½	2	3	4	5	6
1	33	27	6.9	3.6					
2	1.4	3.6	15	16.5	2.1	1.5			
3	5.7	7.6	5.1	2.6	2.0	1.5	6.4	2.7	1.7
4	1.3	3.7	2.9	1.8	1.3	1.6	1.6	2.4	1.4
5	3.9	2.0	1.6	1.3	1.4	1.3	1.8	1.7	2.0
6	8.8	7.8	2.5	1.5	1.3	1.1	1.3	1.5	1.1
7	2.7	9.4	6.0	10.5	3.7	2.0	2.7	6.0	22
8	1.6	2.6	6.0	4.0	1.7	1.4	1.4	1.4	1.3

Effect on Insulin levels

	Time (hrs.)								
No.	0	½	1	1½	2	3	4	5	6
1	13	13	18	13					
2	10	7	10	10	7	40			
3	60	30	26	74	24	170	25	42	20
4	18	30	19	14	26	50	36	39	32
5	16	17	21	20	75	75	48	70	42
6	22	22	23	18	115	88	52	58	58
7	36	24	21	30	37	38	27	20	24
8	17	18	18	24	18	64	43	24	31

Effect on cortisol level

	Time (hrs.)								
No.	0	½	1	1½	2	3	4	5	6
1	18.5	15	12						
2	11.5	32.5	26.5		12.5				
3	15.5	14	11		9.5				
4	16.5	12	15		13.5				
5	13.5	13.5	21		15.5		7.0		
6	16.5	13.5	11.5		12.0		16.0		
7	18.0	12.5	24.0		24.0		18.5		
8	16	13.5	12.0		18.0		12.0		

Effect on Thyroxine iodine levels

	Time (hrs.)								
No.	0	½	1	1½	2	3	4	5	6
1	4.3		3.8						
2	4.5		4.6		4.5				
3									
4									
5	3.7		4.0		3.9		3.9		
6	3.6		3.6		3.4		3.3		
7	4.5		5.5		5.0		5.2		
8	5.1		5.5		5.4		5.6		

Effect on blood glucose

	Time (hrs.)								
No.	0	½	1	1½	2	3	4	5	6
1	60	70	60	75					
2	70	60	55	55	60	65			
3	60	65	70	75	50	95	60	70	70
4	65	60	70	60	70	85	75	75	70
5	70	65	65	70	85	75	80	85	80
6	80	60	60	55	85	85	80	70	55
7	70	70	55	60	80	80	65	60	75
8	70	60	55	65	65	60	65	65	90

Effect on L.H. (milli.I.U/ml.)

	Time (hrs.)								
No.	0	½	1	1½	2	3	4	5	6
1	6	5	5	5					
2	3	6	4	3	5				
3	5	5	5	5	6	5	6	4	
4	7	6	7	7	7		7	9	7
5	3	5	5	4	6	6	5	9	6
6	2	2	1	5	3	2	3	2	7
7	ND	1	5	4	3	2	2	1	2
8	1	1	1	3	3	1	1	6	2

ND = not detected i.e. less than 1 m. I.U./ml.

Effect on F.S.H. (milli.I.U./ml.).

	Time (hrs.)								
No.	0	½	1	1½	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 1½ hours but fainted at 2 hours.
2	Flushing and slight nausea noted at 10 minutes.
3	Flushing and slight nausea noted at 1½ - 3½ hours.
4	Nausea present ½ - 3 hours.
5	Nausea 30 minutes. Vomited at 45 minutes.
6	Marked nausea 1 - 1½ hours.
7	Flushed, sweating and restless at 1 hour. Nausea throughout.
8	Sweating at 1 hour.

CONCLUSIONS

(1) ICI 63,197 did not have any significant effect upon any parameters measured, in the setting of the study.

(2) Every subject experienced some type of adverse reaction, especially nausea and flushing.

EFFECT OF ICI 63,197 UPON ORAL & INTRAVENOUS GLUCOSE TOLERANCE TESTS

DR. D. DAVIES, MANCHESTER.

PROTOCOL

Two fit, healthy young volunteers were chosen. They gave informed consent to taking part in the study. They underwent a glucose tolerance test (GTT) on 4 occasions each. Twice the GTT was an oral one, once with a placebo tablet and once with a single dose of 2 mg. ICI 63,197, and on the other two occasions the GTT was an intravenous one, again both with placebo and 2 mg. ICI 63,197. Tests were carried out at 7 day intervals.

Blood samples were taken 60 mins., 30 mins. and immediately before the glucose load was given and for the intravenous test 2, 5, 10, 20, 30, 40 and 60 minutes after, and for the oral test 30, 60, 90, 120 and 150 minutes after.

Blood samples were assayed for:-

(a) Glucose

(b) Insulin

(c) Free fatty acid levels.

Possible side effects were noted.

RESULTS

Two male subjects were studied.

Oral GTT

Effect of Glucose levels

		Time (mins.)							
No.	Regime	-60	-30	0	30	60	90	120	150
1	Placebo	80	75	70	100	130	80	45	45
1	Active	75	80	65	110	95	75	70	75
2	Placebo	35	35	65	100	70	60	40	45
2	Active	60	55	55	65	85	70	60	60

Effect on Insulin levels

		Time (mins.)							
No.	Regime	-60	-30	0	30	60	90	120	150
1	Placebo	16	16	13	76	125	35	18	14
1	Active	14	18	16	56	44	16	14	16
2	Placebo	18.5	15.5	14	84	92	54	52	18
2	Active	12	12	14.5	12	47	52	32	22.5

Effect on FFA levels (mEq/l)

		Time (mins.)							
No.	Regime	-60	-30	0	30	60	90	120	150
1	Placebo	2.24	2.24	2.12	2.67	1.00	1.05	1.24	1.90
1	Active	1.17	1.03	1.08	1.01	0.61	1.08	2.34	2.09
2	Placebo	0.80	0.69	0.93	1.42	0.74	0.77	0.83	1.09
2	Active	1.14	1.59	1.64	2.27	3.18	0.89	0.73	0.93

Intravenous GTT

Effect on Glucose levels

		Time (mins.)									
No.	Regime	-60	-30	0	2	5	10	20	30	40	60
1	Placebo	55	55	65	165	165	155	140	110	95	70
1	Active	75	75	70	215	175	170	145	115	100	75
2	Placebo	65	60	60	130	140	145	120	90	75	60
2	Active	65	70	70	315	250	230	200	175	155	115

Effect on Insulin levels

		Time (mins.)									
No.	Regime	-60	-30	0	2	5	10	20	30	40	60
1	Placebo	19	18	20	53	45	40	34	34.5	34.5	27
1	Active	17	20	17	52	62	56	62	52	52	25.5
2	Placebo	13	9.4	9.4	31	70	44	33	33	31	20
2	Active	7.8	9.4	9.4	7.8	9.4	14	33	41	51	44

Effect on FFA levels (mEq/l)

		Time (mins.)									
No.	Regime	-60	-30	0	2	5	10	20	30	40	60
1	Placebo	0.99	1.28	1.39	1.31	1.28	1.31	0.83	0.54	0.51	0.48
1	Active	1.84	1.82	1.82	2.0	1.86	1.91	1.68	1.05	1.09	0.9
2	Placebo	0.81	0.88	0.93	1.41	1.29	1.31	1.29	1.52	1.14	1.29
2	Active	1.55	1.20	1.22	1.73	1.83	1.97	2.25	1.69	1.50	0.78

Possible side effects

No side effects were seen.

CONCLUSIONS

Although only 2 subjects were used, ICI 63,197 seemed to suppress the insulin rise following the glucose load in both subjects in the oral test.

EFFECT OF ICI 63,197 IN HISTAMINE INDUCED BRONCHOSPASM IN ASTHMATIC PATIENTS

(DR. J.W. KERR, GLASGOW)

PROTOCOL

Allergic asthmatic patients with reversible airways obstruction were chosen for the study. Pregnant women and patients under 18 or over 45 years were excluded.

Patients were studied on the occasions when they took either ICI 63,197 2 mg. orally, or an identical placebo tablet, in a double blind randomised fashion. 2 hours later, bronchospasm was induced with an intravenous injection of histamine, and the forced expiratory volume in seconds (FEV_1) and the vital capacity were measured before and at 5, 10, 15, 20 and 25 minutes thereafter.

A note of possible side effects were made.

RESULTS

Details of patients studied

No.	Initials	Age (yrs)	Sex	Diagnosis
1	AS	60	M	"pollen asthma"
2	DI	22	M	hay fever and asthma
3	ED	22	F	asthma
4	IN	41	M	asthma

Effect on FEV_1 (litres)

No.	Time after i/v histamine (mins.)											
	Placebo						ICI 63,197					
	0	5	10	15	20	25	0	5	10	15	20	25
1	1.90	1.70	1.70	1.75	1.80	1.90	2.0	1.80	1.70	1.80	2.00	2.00
2	4.15	4.45	4.20	4.00	4.65	4.70	4.50	4.50	4.50	4.30	4.40	4.40
3	0.65	0.70	0.65	0.65	0.65	0.65	0.75	0.55	0.50	0.50	0.50	0.65
4	1.80	1.45	1.30	1.30	1.90	1.90	1.65	0.8	0.75	0.8	0.8	0.8

Effect on vital capacity (litres)

No.	Time after i/v histamine (mins.)											
	Placebo						ICI 63,197					
	0	5	10	15	20	25	0	5	10	15	20	25
1	3.70	3.50	3.55	3.70	3.80	3.80	3.60	3.50	3.50	3.50	3.60	3.60
2	5.60	5.40	5.15	5.20	5.65	5.60	5.50	5.30	5.30	5.30	5.35	5.40
3	1.50	1.45	1.50	1.50	1.50	1.50	1.50	1.30	1.16	1.15	1.15	1 25
4	3.40	3.05	2.75	2.60	2.60	2.60	2.10	1.90	1.90	2.05	2.05	2.10

Possible side effects

Two patients complained of nausea following ingestion of ICI 63,197 and one was sick. No side effects were noted during the placebo periods.

CONCLUSIONS

No evidence was obtained from these 4 patients to show that ICI 63,197 gave any protection from the falls in FEV_1 and VC induced by intravenous histamine.

EFFECT OF ICI 63,197 WITH AND WITHOUT SALBUTAMOL UPON FORCED EXPIRATORY VOLUME IN ASTHMATICS. (DR. K.N.V. PALMER, ABERDEEN).

PROTOCOL

Asthmatic patients between the ages of 18 and 45, who had reversible airways obstruction, were included in the study. Pregnant women were excluded. The aim of the study was to look for possible potentiation of the effect of salbutamol upon bronchospasm induced by an aerosol of histamine.

Patients were seen on 4 occasions, when one of the following were given:-

a) 2 mg. salbutamol

b) 2 mg. ICI 63,197

c) 2 mg. salbutamol + 2 mg. ICI 63,197

d) placebo.

Drugs were given in a double blind manner in random sequence. Two hours after taking the tablet a dose of histamine by aerosol was given. This dose had been previously determined as one that would produce a measurable bronchospasm.

Before and at 1, 5, 15 and 30 minutes after the histamine the forced expiratory volume in 1 second (FEV_1), pulse rate and blood pressure were measured.

RESULTS

Only 2 patients were included in the study as in the second severe side effects occurred.

Details of the patients studied

No.	Initials	Age (yrs)	Sex	Weight (kg)
1	RR	32	M	71
2	DW	34	M	70

Effect upon FEV_1 (litres)

Patient No. 1

	Histamine challenge (time in mins.)				
Regime	0	1	5	15	30
placebo	2.75	1.7	1.75	2.4	2.65
ICI 63,197	2.95	3.25	3.75	3.70	3.90
salbutamol	2.8	4.0	4.05	4.05	4.10
combination	2.55	2.10	2.10	2.65	2.95

Patient No. 2

	Histamine challenge (time in mins.)				
Regime	0	1	5	15	30
placebo	2.45	1.25	1.25	1.30	1.32
ICI 63,197	3.15	2.2	2.25	2.72	3.0

Effect on pulse rate (beats/min.)

Patient No. 1

	Histamine challenge (time in mins.)				
Regime	0	1	5	15	30
placebo	88	80	76	72	70
ICI 63,197	64	60	60	66	64
salbutamol	68	72	72	72	72
combination	76	56	58	60	60

Patient No. 2

	Histamine challenge (time in mins.)				
Regime	0	1	5	15	30
placebo	76	93	88	80	72
ICI 63,197	64	76	84	80	76

Effect on blood pressure

Patient No. 1

	Histamine challenge (time in mins.)				
Regime	0	1	5	15	30
placebo	115/80	115/80	110/75	105/65	110/65
ICI 63,197	110/55	110/60	110/60	110/60	110/60
salbutamol	110/55	110/60	110/60	110/60	110/60
combination	120/70	120/70	120/70	120/75	120/80

Patient No. 2

	Histamine challenge (time in mins.)				
Regime	0	1	5	15	30
placebo	110/75	125/75	110/70	105/65	100/65
ICI 63,197	110/70	120/80	120/80	110/75	110/70

Possible side effects

Patient No. 1 had no side effects during the study. Patient No. 2 took ICI 63,197 at the first sitting. 20 minutes after ingestion the patient complained of severe nausea, followed by copious vomiting. The patient was markedly agitated and restless and became pale, cold and clammy. These features slowly wore off over the next 2 hours. Because of these symptoms this patient was not given ICI 63,197 on a second occasion and the triallist was unwilling to expose further patients.

CONCLUSIONS

In both patients there was some evidence that the effect of histamine upon FEV_1 was reduced by ICI 63,197. In the one patient taking salbutamol there was clear protection against histamine bronchospasm but when combined with

ICI 63,197 this effect of salbutamol disappeared. The data is insufficient to draw any conclusions.

Severe nausea and vomiting occurred in one patient.

EFFECT OF ICI 63,197 ON THE EFFECTS OF INHALED ISOPRENALINE (DR.H.BEUMER, UTRECHT)

PROTOCOL

Patients with mild/moderate emphysema who were known to respond to inhaled isoprenaline by bronchodilatation were chosen for the study. They were tested on two occasions, upon which they took either a single dose of ICI 63,197 or an identical placebo in random order, double blind. Measurements were done on each occasion as follows:-

Time (mins.)	
0	ICI 63,197 or placebo tablet given.
60	Pulse rate, nitrogen washout and functional reserve capacity measured.
90	Pulse rate, nitrogen washout and functional reserve capacity measured.
120	As at 90 mins.

RESULTS

12 patients were studied.

Effect on pulse rate

* = time after isoprenaline inhalation

	Placebo			ICI 63,197		
No.	Control	30 mins.*	60 mins.*	Control	30 mins.*	60 mins.*
1	80	84	84	72	70	72
2	76	84	80	80	84	84
3	84	80	76	84	88	80
4	60	52	60	68	64	60
5	72	72	68	80	72	80
6	68	64	72	86	60	68
7	92	92	88	100	88	80
8	80	84	80	96	96	96
9	84	76	76	84	84	84
10	80	72	76	80	72	72
11	96	100	88	96	88	88
12	120	120	120	124	124	118

Effect on Nitrogen washout

* = time after isoprenaline inhalation

	Placebo			ICI 63,197		
No.	Control	30 mins.*	60 mins.*	Control	30 mins.*	60 mins.*
1	64.0	64.0	64.0	64.0	64.0	64.0
2	64.0	64.0	64.0	63.9	64.0	64.0
3	64.0	64.0	63.9	64.0	64.0	64.0
4	48.2	47.4	55.1	54.0	64.0	55.2
5	64.0	64.0	64.0	64.0	64.0	64.0
6	64.0	57.6	55.9	64.0	58.9	55.4
7	27.5	26.7	25.7	28.0	29.3	25.3
8	64.0	64.0	64.0	64.0	64.0	64.0
9	64.0	64.0	64.0	64.0	63.9	64.0
10	64.0	64.0	64.0	64.0	64.0	64.0
11	64.0	64.0	64.0	64.0	64.0	64.0
12	64.0	64.0	64.0	64.0	64.0	64.0

Effect on functional reserve capacity

	Placebo			ICI 63,197		
No.	Control	30 mins.	60 mins.	Control	30 mins.	60 mins.
1	6.57	6.61	6.60	5.77	6.22	5.95
2	4.57	5.34	5.30	5.05	4.83	4.27
3	5.22	5.09	5.51	5.78	5.04	5.56
4	4.36	4.40	4.54	5.12	5.27	4.65
5	6.55	6.24	6.60	6.39	6.16	6.20
6	4.70	4.26	4.41	4.82	4.17	4.20
7	2.60	2.48	2.57	2.38	3.30	2.72
8	6.69	5.69	6.43	6.30	6.25	6.48
9	4.99	4.58	4.62	5.17	5.09	5.13
10	5.24	4.57	4.97	4.93	4.66	4.97
11	6.69	6.88	6.81	6.65	6.84	6.71
12	4.16	4.43	4.43	4.19	4.25	4.39

CONCLUSIONS

No effect of ICI 63,197 was demonstrated over and above placebo upon pulse rate, functional reserve capacity and nitrogen washout after the inhalation of isoprenaline. However, it must be noted that no effect of isoprenaline per se was detected. This is probably due to the fact that the first measurement at 30 minutes after inhalation was too late.

EFFECT OF ICI 63,197 IN ENDOGENOUS DEPRESSION (DR. D. ECCLESTON, EDINBURGH)

PROTOCOL

Patients with classical endogenous depression who were not on any other medication were chosen for the study. Patients under the age of 18 or over 60 were excluded. Patients were given 2 mg. ICI 63,197 TDS for 21 days and were to leave the trial at that time if no beneficial effect had been seen.

Depression was rated (Hargreaves scale) daily, as were possible side effects.

RESULTS

4 patients completed 21 days treatment each. The trial was then abandoned, due to side effects and a worsening of depression in all 4 patients, apparently due to ICI 63,197.

Detailed results are not available, but the triallist reported the following:-

(1) All 4 patients became markedly worse over the 21 days of treatment. This worsening was considered more than would be expected from the natural history of their respective illnesses. They were all given ECT on stopping ICI 63,197.

(2) In one patient the effect of ECT was considered to be greater than expected from the patient's clinical state.

(3) All 4 patients complained of nausea in the first 3 - 5 days of the trial, although this were off with no intervention.

(4) One patient developed a tendency to bruise with a positive Hess's test. The agent was withdrawn whereupon the capillary fragility disappeared over the next 3 - 4 days.

ICI 63,197 IN SCHIZOPHRENIA (DR. R.V. MAGNUS, BIRMINGHAM)

PROTOCOL

Chronic inpatient schizophrenics were chosen for the study upon the basis that they had sufficient symptomatology to show a significant change. Patients under 18 or over 50 years of age were excluded, as were pregnant women and people with physical illness.

Patients were given 1 placebo tablet TDS for 6 days, followed by 1 mg. ICI 63,197 (1 x 1 mg. tablet) TDS for 7 days, followed by 2 mg. ICI 63,197 (1 x 2 mg. tablet) TDS for 7 days if the agent was tolerated. All tablets were identical.

On entry to the trial, the following were recorded:-

(a) age, sex, weight

(b) diagnosis

(c) rating of schizophrenia

(d) blood sample for Hb, WBC, diff. ESR, urea, bilirubin, alkaline phosphatase and SGOT.

On days 6, 13 and 20, the following were recorded:-

(a) rating of schizophrenia

(b) clinical assessment

(c) possible side effects

(d) pulse rate and blood pressure

(e) blood sample for the tests mentioned above.

RESULTS

Details of patients studied

No.	Initials	Age (yrs)	Sex	Weight (kg)	Diagnosis
1	CJT	19	M	140	Schizo-affective disorder
2	MW	19	M	156	High grade sub-normal with chronic schizophrenia
3	FM	49	M	112	Chronic paranoid schizophrenia
4	WJ	54	M	150	Chronic schizophrenia
5	WH	52	M	-	Paranoid schizophrenia
6	SP	28	F	112	Chronic hebephrenic schizophrenia

Effect on clinical state

No patient showed any significant change in their schizophrenic state. Their rating scores are shown below:-

No.	Day 0	Day 6[1]	Day 13[2]	Day 20[3]
1	15	13	12	12
2	13	13	13	10
3	9	9	9	12
4	16	17	11	11
5	14	14	14	12
6	21	21	20	25

1 = end of 6 day placebo period

2 = end of 7 days at 1 mg. ICI 63,197 TDS

3 = end of 7 days at 2 mg. ICI 63,197 TDS

Possible side effects

These are shown below:-

No.	Possible side effects
1	Nil
2	Slight nausea at 2 mg. TDS
3	Marked nausea at 2 mg. TDS
4	Nil
5	Nil
6	Nil

Effect on pulse and B.P.

These are shown below:-

Pulse (beats/min.)

No.	Day 0	Day 6	Day 13	Day 20
1	80	72	80	72
2	80	72	72	72
3	80	80	72	80
4	80	72	72	72
5	72	72	80	80
6	80	-	100	100

B.P. (mmHg)

No.	Day 0	Day 6	Day 13	Day 20
1	120/70	120/70	130/70	140/75
2	130/75	120/70	120/70	130/80
3	130/90	120/70	120/70	130/70
4	130/80	120/70	130/70	130/80
5	135/70	120/70	140/80	130/70
6	130/70	-	130/70	130/80

Effect on blood tests

No significant effect was seen upon Hb, WBC, diff. ESR, urea, bilirubin, alkaline phosphatase or SGOT.

CONCLUSIONS

(1) ICI 63,197 had no effect upon the schizophrenic state.

(2) ICI 63,197 had no significant effect upon pulse rate, blood pressure on the blood tests used.

(3) 2 out of 6 patients complained of nausea at 2 mg. ICI 63,197 TDS.

ICI 63,197 IN ANXIETY STATES (DR. R.V. MAGNUS, BIRMINGHAM)

PROTOCOL

Inpatients with established anxiety states were selected for the study. Those under 18 or over 50 years of age were excluded, as were pregnant women and people with overt physical illness.

Patients were given 1 placebo tablet TDS for 5 days, followed by 1 mg, ICI 63,197 (1 x 1 mg. tablet) TDS for 7 days, followed by 2 mg. ICI 63,197 (1 x 2 mg. tablet) TDS for 7 days, if the patient could tolerate it. All tablets were identical.

On entry to the trial the following were recorded:-

(1) age, sex, weight

(2) diagnosis

(3) severity of anxiety

(4) anxiety rating using the Taylor Manifest Anxiety Scale

(5) blood sample for Hb, WBC, diff.ESR, urea, bilirubin, alkaline phosphatase and SGOT.

At the 5th, 12th and 19th days the following were recorded:-

(1) Taylor Manifest Anxiety score

(2) clinical assessment

(3) pulse rate and blood pressure

(4) possible side effects

(5) blood sample for tests above

RESULTS

Details of patients studied

No.	Initials	Age (yrs)	Sex	Weight (kg)	Diagnosis	Rating of anxiety
1	VM	18	M	154	Anxiety state	Severe
2	AC	32	F	112	Anxiety state	Moderate
3	MN	24	F	116	Anxiety state	Moderate
4	RT	44	F	120	Anxiety state with obsession	Severe
5	KH	22	M	130	Anxiety state	Moderate

Effect on anxiety

Clinically, patients No. 1 and 5 became somewhat worse on ICI 63,197, patients No. 2 and 3 showed n o change while patient No. 4 showed an improvement. The Taylor scores are shown below:-

No.	Day 0	Day 5[1]	Day 12[2]	Day 19[3]
1	31	31	39	39
2	1[illegible]	22	23	23
3	29	29	29	25
4	36	35	29	16
5	[illegible]7	22	[illegible]6	25

1 = end of placebo period
2 = end of 1 mg. TDS for 7 days
3 = end of 2 mg. TDS for 7 days

Possible side effects

These are shown below:-

No.	Possible side effect
1	Vomited x 1 on 2 mg. TDS. Then settled.
2	Nil
3	Nil
4	Nausea on 2 mg. TDS. Maxolon 10 mg. TDS given with good effect
5	Nausea on 2 mg. TDS. Maxolon 10 mg. TDS given with good effect

Effect on pulse and blood pressure

Pulse rate and B.P. throughout the study are shown below:-

Pulse rate (beats/min.)

No.	Day 0	Day 5	Day 12	Day 19
1	80	80	88	80
2	100	80	80	80
3	80	80	72	72
4	88	-	80	72
5	88	72	88	80

B.P. (mmHg)

No.	Day 0	Day 5	Day 12	Day 19
1	140/80	130/70	130/70	130/70
2	130/70	130/70	130/70	130/70
3	120/70	120/70	110/70	110/70
4	140/70	130/70	130/70	120/70
5	130/80	120/70	130/70	130/70

Blood tests

No significant changes were seen in the values of Hb, WBC, diff. ESR, bilirubin, alkaline phosphatase, urea, and SGOT during this study.

CONCLUSIONS

(1) ICI 63,197 did not significantly affect anxiety

(2) ICI 63,197 did not significantly affect pulse rate, blood pressure or the blood tests used.

(3) ICI 63,197 produced nausea or vomiting in 3 out of 5 patients, all at 2 mg. TDS.

ICI 63,197 IN HYPERTENSION (DR. F.J. ZACHARIAS, EBBINGTON)

PROTOCOL

Patients with a sustained diastolic hypertension in the range 100 - 115 mmHg were chosen for the study. They were to be on no other drugs Patients under 18 or over 60 years of age, and pregnant women were excluded.

Patients took ICI 63,197 2 mg. QDS for 4 weeks in the first instance, and this could be continued as clinically indicated.

On entry to the trial, the following were recorded:-

(a) age, sex, weight

(b) diagnosis

(c) blood pressure (standing and lying)

(d) blood sample for Hb, WBC, diff.ESR, bilirubin, alkaline phosphatase SGOT and urea.

At weekly intervals through the trial the following were recorded:-

(a) blood pressure

(b) body weight

(c) possible side effects

(d) the blood tests mentioned above.

RESULTS

Details of patients studied

No.	Initials	Age (yrs)	Sex	Weight (kg)	Diagnosis
1	CCS	45	M	85.0	Hypertension
2	RJT	-	M	67.7	Essential hypertension with asthma
3	SN	64	M	77.3	Essential hypertension

Effect on blood pressure

The standing B.P.s (mmHg) during treatment with ICI 63,197 are shown below. There was no significant difference between standing and lying B.P.

	Week of treatment												
No.	0	1	2	3	4	5	6	7	8	9	10	11	12
1	180/110	150/100	145/95	165/100	145/100	150/95							
2	210/115	180/110	175/110	195/115	180/115	180/120	165/105	220/115					
3	125/115	180/115	180/105	165/110	170/110	175/110	165/105	150/105	170/110	165/105	170/110	175/110	180/115

Effect upon body weight

No significant change was seen in body weight during treatment with ICI 63,197.

Possible side effects

These are shown below:-

No.	Possible side effects
1	Nil
2	Severe indigestion, dizziness, flushing. Eventually refused to continue.
3	Nausea, severe heartburn, flushing. Agent finally stopped due to side effects.

Effect on blood tests

No significant change was seen in Hb, WBC, diff.ESR, bilirubin, alkaline phosphatase, SGOT or urea.

CONCLUSIONS

(1) ICI 63,197 did not significantly affect the B.P. of these hypertensive subjects.

(2) There was no effect on body weight on the blood tests used.

(3) 2 of the 3 had severe gastrointestinal side effects with dizziness and flushing.

EFFECT OF ICI 63,197 IN OBESE SUBJECTS

DR. D. DAVIES, MANCHESTER.

PROTOCOL

Patients in the age range 30 - 55 years with a body weight at least 30% over the ideal for their age, sex, height and build, were selected for the study. The trial was a double blind cross-over study of ICI 63,197 2 mg. TDS against identical placebo tablets given TDS, 6 weeks each. Patients were reviewed at fortnightly intervals when body weight, skin fold thickness, pulse rate and blood pressure were noted. A record of possible side effects was kept. Blood samples were taken at each visit for haemoglobin, white cell count, differential count, ESR, platelet count, bilirubin, alkaline phosphatase, SGOT, SGPT, Albumin, Globulin and urea. Urine was also checked for the possible presence of sugar, protein or blood.

RESULTS

Four patients had entered the study before it was discontinued, due to the appearance of angina pectoris in two patients while on the active preparation.

Details of patients studied

No.	Initials	Age (yrs)	Sex	Weight (kg)
1	SMcK	19	M	142.4
2	MT	50	F	166.0
3	AT	38	F	101.8
4	BA	33	F	83.0

Effect on body weight

No.	Baseline	Placebo			Active		
		Week 2	Week 4	Week 6	Week 2	Week 4	Week 6
1	142.4	134.0	134.8	134.2	140.6	138.0	138.0
2	166.0			163.7	161.0	161.0	160.6
3	101.8				103.8	106.2*	
4	83.0				82.0	82.8	83.3*

* trial stopped due to appearance of angina

Effect on skin fold thickness (cms.)

No.	Baseline	Placebo			Active		
		Week 2	Week 4	Week 6	Week 2	Week 4	Week 6
1	R3.1 L3.3	R2.7 L3.1	R2.7 L3.0		R2.9 L3.1		R2.8 L3.1
2	2.2	2.2		2.0	1.9	2.1	2.1
3	R3.0 L3.1				R3.2 L3.1*		
4	R3.0 L2.8				R3.0 L2.9	R2.7 L2.7	R2.7 L2.7*

* trial stopped due to appearance of angina
R = right arm
L = left arm

Effect on pulse rate (beats/min.)

No.	Baseline	Placebo			Active		
		Week 2	Week 4	Week 6	Week 2	Week 4	Week 6
1	84	72			56	72	60
2	80	88		96	80	72	80
3	80				88	80*	
4	72				64	72	72*

* trial stopped due to appearance of angina

Effect on blood pressure (mmHg)

No.	Baseline	Placebo			Active		
		Week 2	Week 4	Week 6	Week 2	Week 4	Week 6
1	120/80	115/80	130/70		120/80	130/75	115/80
2	190/100	200/110		120/80	170/100	150/100	190/110
3	145/85				120/80	110/80	
4	110/70				110/70	110/70	120/75

Effect on blood tests

No abnormality was detected in Hb, WBC, diff. ESR, platelets, bilirubin, alkaline phosphatase, SGOT, SGPT, albumin, globulin or urine during the study.

Effect on urine tests

No abnormal urine findings were detected during the study.

Possible side effects

Three patients (Nos. 1, 2 and 4) complained of marked dyspepsia, flatulence and nausea while taking the active agent. In two patients (Nos. 3 and 4) classical angina of effort appeared for the first time ever while on the active regime. For this reason, the trial was abandoned.

Neither patient who took the placebo run had any side effects while on that regime.

CONCLUSIONS

As far as a possible anti-obesity effect is concerned this trial is inadequate to draw any conclusions. No effect was seen on pulse rate or blood pressure and blood and urine tests remained normal. Upper gastrointestinal

side effects were marked with the agent. The appearance of angina pectoris in two patients who had never had this symptom and in whom the cardiovascular system was clinically normal was apparently due to the compound. This view is strengthened by the fact that since withdrawal no more attacks have been recorded even on severe exercise. The mechanism whereby this was produced must be speculative but it could be due to the potentiation of endogenous catecholamines by ICI 63,197 on exercise, or perhaps the mobilisation of free fatty acid which could increase myocardial oxygen requirements.

From
Dr J R Heylings
Biochemical Toxicology

ICI Central Toxicology Laboratory

Alderley Park
Macclesfield Cheshire SK10 4TJ

Tel: 0625 582711
Telex: 669095/669388
Fax: 0625 582897

To
L L Smith

Copies to
S E Jaggers
R S Morrod

Your ref	Our ref	Direct line	Tel ext	Date
	JRH007/LCM	0625 514550	4550	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 does 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 toxicolgical 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))
PP796 = 0.5mg/kg (effective)) SURVIVAL

GRAMOXONE EXPORT (20% PQ + 0.05% PP796)

PQ: Emetic ratio = 400

PQ Dose = 20mg/kg (lethal))
PP796 = 0.05mg/kg (ineffective)) DEATH (IRI STUDY 1987)

Dogs would require a minimum of 10 x 20 = 200mg/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)
PP796 Dose = 0.22mg/kg (ineffective)
DEATH (IRI STUDY)

Bipyridyl dose = 20mg/kg (lethal)
PP796 Dose = 0.11mg/kg (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	-	-
4	0.06	2	1/2	50
8	0.11	1	1/1	100

* Carried out but not stated in report.
(<- What if 0/1?)

JRH 1990
Ref JRH007/Lcm

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 by tablet compared to solution	- 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 would enhance vomiting response"	- No rationale for this at all. PQ induced vomiting takes several hours. Time to vomiting is central to the argument.
(ii)	"Soluble dispersed form is more bioavailable than solid"	- Not proven and extremely unlikely 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 Jaggers
Regulatory Toxicology Manager

ICI Central Toxicology Laboratory

Alderley Park
Macclesfield Cheshire SK10 4TJ

Tel: 0625 582711
Telex: 669095/669388
Fax: 0625 582897
EDT: UKBLA99::SEJ1

To
Dr J R Heylings
Biochemical Toxicology

Copies to
Dr R S Morrod
Dr L L Smith

Your ref	Our ref	Direct line	Tel ext	Date
	SEJ/LMM	0625 512818	2818	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 Jaggers

From
Dr J R Heylings
Biochemical Toxicology

ICI Central Toxicology Laboratory

Alderley Park
Macclesfield Cheshire SK10 4TJ

Tel: 0625 582711
Telex: 669095/669388
Fax: 0625 582897

To
Dr S E Jaggers
Research Toxicology Manager

Copies to
L L Smith

Your ref	Our ref	Direct line	Tel ext	Date
	JRH009/LCM	0625 514550	4550	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
Reumer	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 J R Heylings
Biochemical Toxicology

ICI Central Toxicology Laboratory

Alderley Park
Macclesfield Cheshire SK10 4TJ

Tel: 0625 582711
Telex: 669095/669388
Fax: 0625 582897

To
Dr. L.L. Smith
Head, Biochemical Toxicology

Copies to

Your ref	Our ref	Direct line	Tel ext	Date
	JRH059/SCI	0625 514550	4550	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.

Jon R. Heylings

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

From

Dr L L Smith
Biochemical Toxicology

To

Dr J R Heylings
Biochemical Toxicology

ICI Central Toxicology Laboratory

Alderley Park
Macclesfield Cheshire SK10 4TJ

Tel: 0625 582711
Telex: 669095/669388
Fax: 0625 582897

Copies to

Dr S E Jaggers

Your ref	Our ref	Direct line	Tel ext	Date
	LLS409/JJB	0625 512878	2878	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

Lewis Smith

From

Dr L L Smith
Biochemical Toxicology

ICI Central Toxicology Laboratory

Alderley Park
Macclesfield Cheshire SK10 4TJ

Tel: 0625 582711
Telex: 669095/669388
Fax: 0625 582897

To

J R Heylings
Biochemical Toxicology

Copies to

Dr S E Jaggers

CONFIDENTIAL

Your ref	Our ref	Direct line	Tel ext	Date
	LLS438/JJB	0625 512878	2878	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 suportive 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 J R Heylings
Biochemical Toxicology

ICI Central Toxicology Laboratory

Alderley Park
Macclesfield Cheshire SK10 4TJ

Tel: 0625 582711
Telex: 669095/669388
Fax: 0625 582897

To
Dr S E Jaggers
Executive Group

Copies to

Your ref	Our ref	Direct line	Tel ext	Date
	JRH101/LCM	0625 514550	4550	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 R. Heylings

DR J R HEYLINGS
Biochemical Toxicology

From
Dr S E Jaggers
Regulatory Toxicology Manager

ICI Central Toxicology Laboratory

Alderley Park
Macclesfield Cheshire SK10 4TJ

Tel: 0625 582711
Telex: 669095/669388
Fax: 0625 582897
Directorate Fax: 0625 590250
EDT: UKBLA99::SEJ1

To
Dr G J A Oliver

Copies to
Dr J R Heylings
Dr R C Scott

Your ref	Our ref	Direct line	Tel ext	Date
	SEJ/LMM	0625 512818	2818	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 Jaggers

From
Dr S E Jaggers
Regulatory Toxicology Manager

ICI Central Toxicology Laboratory

Alderley Park
Macclesfield Cheshire SK10 4TJ

Tel: 0625 582711
Telex: 669095/669388
Fax: 0625 582897
Directorate Fax: 0625 590250
EDT: UKBLA99::SEJ1

To
Dr J R Heylings

Copies to

Your ref	Our ref	Direct line	Tel ext	Date
	SEJ/LMM	0625 512818	2818	26 Apr 91

John,

EMETIC INCLUSION LEVELS

Thank you for your letter of the 9th April and the background information. It is quite routine for the Laboratory to review its data base on any topic from time to time and I confirm that I believe the time is appropriate to review the Laboratory recommendations on the inclusion level of the emetic PP796 in Gramoxone

As you state in your letter it is important that we provide the very best advice at this point as the Business is considering sanctioning a new emetic plant. It is my initial impression that the review will not change the direction of the existing CTL recommendation but alter the force with which the case can be put.

After briefly reading the papers that you sent me and some of the past exchanges of letters on the subject I must re-emphasize my view that any review must be positive - in the sense that it is conducted looking forward. I believe it will always be difficult to look back over 15 years and decide whether a decision was misleading or prudently conservative - particularly when it was not made with the benefit of your own data.

Nevertheless I am committed to a re-evaluation of all the existing pertinent data. From our discussion I know you have your own clear opinions. In order to provide an overview I have asked Dr Oliver to chair a small team consisting of your self and Dr Scott (as Paraquat Product Manager) to address the existing data. He has accepted the task. I am writing separately to Dr Oliver to initiate the process formally.

S E Jaggers

From
Dr J R Heylings
Biochemical Toxicology

ICI Central Toxicology Laboratory

Alderley Park
Macclesfield Cheshire SK10 4TJ

Tel: 0625 582711
Telex: 669095/669388
Fax: 0625 582897

To
G A Willis
N N Sabapathy

Copies to
PSAC Sub-committee members

R C Scott	G J A Oliver
T Green	J W Botham
E A Lock	S E Jaggers
R S Morrod	

Your ref	Our ref	Direct line	Tel ext	Date
	JRH111/JJB	Redacted - EU PII	[redacted]	12 June 1991

PARAQUAT HUMAN DATA

Over the past few months I have been collating data on paraquat human poisonings from various internal and external publications in order to gauge the potential impact of reducing the oral toxicity of the herbicide. This data represents a significant proportion of reliable information from 1979-1990 and represents territories where clinical data has been accurately documented (see Table). As a result the database does not include third world territories where paraquat poisoning has also been documented.

I have analysed the data for three primary parameters: (i) the mortality rate from confirmed paraquat poisonings, (ii) the average amount of paraquat consumed in grammes (based on product concentration) and (iii) the impact of increasing the lethal oral paraquat dose by 5 or 10x on these mortality statistics.

In terms of mortality, the combined data show a 76% mortality rate in the territories which are represented. This figure is compatible with previous figures I have seen reported, both inside and outside the Company.

On consideration of the amount of paraquat ingested, it would appear that the average amount of paraquat ingested is about 10 grammes or about 3 lethal doses, based on data from five separate studies (see Table). I believe this to be at variance with what I understood to be the average lethal doses consumed, ie 10-20 lethal doses for paraquat suicides which represent 95% of all poisoning cases.

In order to comment on the impact of increasing the lethal dose of paraquat on mortality, I have chosen a single subset of data from Japan. This comprehensive set of data from ICI Japan was sent to us in 1988. One hundred paraquat cases were studied in detail. The cases involved different products, all of which contained the emetic PP796. At that time we analysed the data for time-to-emesis versus dose, plasma paraquat versus dose, and effect of product

continued....

dilution (eg Preeglox versus Gramoxone). We are now aware that time-to-emesis should be measured in minutes not hours, and that rapid, but brief, emesis induced by PP796 is totally different from the irritancy-induced prolonged emesis caused by the corrosive effect of paraquat. Furthermore, I believe that a sub-effective dose of emetic PP796 was present in all cases which consumed less than 5 lethal doses of paraquat.

On reviewing this same database, I have examined the distribution of a subset of 69 cases where a reasonably accurate measure of volume and concentration of product ingested was made in order to calculate the grammes of paraquat ingested. In consultation with our statistics department at CTL, I present the data from this study as shown on the attached figures.

Human LD_{50} for Paraquat (Figure 1)

Dividing the population into band widths of 1.5 grammes of paraquat enables an LD_{50} curve to be plotted for the 69 human paraquat poisoning cases. As expected, there is a steep dose response between 0.5 and 2 lethal doses which is a well known feature of paraquat lethality in man and experimental animals. The calculated human LD_{50} for paraquat was 3.1 grammes. Had all the cases involved Gramoxone, this would have been equivalent to about 15ml of product - a widely agreed and previously stated LD_{50} volume. There were seventeen people who ingested less than the LD_{50}. This fits very well with the 25% survival rate observed in the 69 cases.

→ MLD = 50 mg/kg

Volume of Paraquat Ingested (Figure 2)

A cumulative frequency plot was made for the 69 human paraquat poisoning cases. This data fits a polynomial distribution very well (r=0.99). From this curve, the average, or more correctly, the median volume of ingested product was 67ml. The majority of the cases involve a 200g/l product, but also include more dilute products such as Preeglox.

200g/l = 200 mg/ml
67mls = 13400 mg
= 206 mg/kg

Grammes of Paraquat Ingested (Figure 3)

The actual amount of paraquat ingested (based on product strength) was calculated for the same 69 human poisoning cases. A cumulative frequency plot was drawn in order to calculate the average or median amount of paraquat ingested. As shown on Figure 3, the average amount of paraquat ingested was 6.9 grammes. This corresponds to 2.2 x LD_{50}.

Improvement in Oral Toxicity of Paraquat and Estimated Survival (Figure 4)

Data presented in Figures 2 and 3 have used volume and weight of paraquat as the ordinate. By combining the LD_{50} value of 3.1 grammes with the plot of weight of paraquat, the same data can be presented using "number of lethal doses" as the ordinate. Figure 4 therefore shows the proportion of a population which includes any given number of lethal doses of paraquat. Thus, an improvement of 5-fold in oral toxicity would include 75% of cases. These figures may correspond to the respective survival rates for 5 and 10x safening. Likewise, an improvement of 10-fold in oral toxicity would include 90% of cases. This is, of course, assuming that this Japanese database is accurate and representative of the population as a whole. However, there are three features which suggest to me that this data is representative of typical paraquat poisonings. Firstly, the steep sigmoidal

dose curve has many of the characteristic features of paraquat lethal dose plots in animals. Secondly, the calculated human LD_{50} of 3 grammes paraquat is widely accepted. Thirdly, the percentage survival rate (~25%) fits many previously published studies which involve combinations of suicide and accidental poisonings.

Interestingly, if 'Magnoxone' were proven to be 15x safer in man and caused an increase in survival from 24% to 90%, this would not only include all accidental poisonings, but the few cases which do consume 15-20 lethal doses (¾ pint) would probably find the new formulation (with its thickening properties) very difficult to drink.

A particularly important feature of the Japanese data occurs at the lower end of the lethal dose scale. The curve rises steeply between 0 and 5 lethal doses. It includes all accidental poisonings and probably most of the para-suicides. It includes 75% of all paraquat poisoning cases in this study. It therefore suggests that even a 5-fold safety factor such as may be caused by increasing the level of emetic by a factor of 5, would have a considerable and measurable impact on the accidental and suicide poisoning statistics for paraquat.

Jon R. Heylings

Dr J R Heylings
Biochemical Toxicology. CTL

HUMAN PARAQUAT POISONINGS

AUTHOR	YEAR	LOCATION	SPAN	CASES	% MORTALITY	AVERAGE LETHAL DOSES INGESTED
Howard (ICI)	1979	UK	1977	68	60%	2
Bismuth et al	1982	France	1972-81	28	61%	-
Zilker et al	1983	Germany	1974-81	21	76%	-
Hart and Whitehead	1984	UK	1977-83	210	78%	3
Proudfoot et al	1987	UK	1986	23	65%	-
Ohno (ICI Japan)	1987	Japan	1986-7	69	75%	2-3
Suzuki et al	1989	Japan	1988	51	84%	-
Yamaguchi et al	1990	Japan	1981-7	160	80%	5
Houzé et al	1990	France	1984-8	17	82%	1-2

Combined data : 490 mortalities from 647 cases (76%)

Fig 1.

JAPANESE HUMAN DATA (1986 – 7)

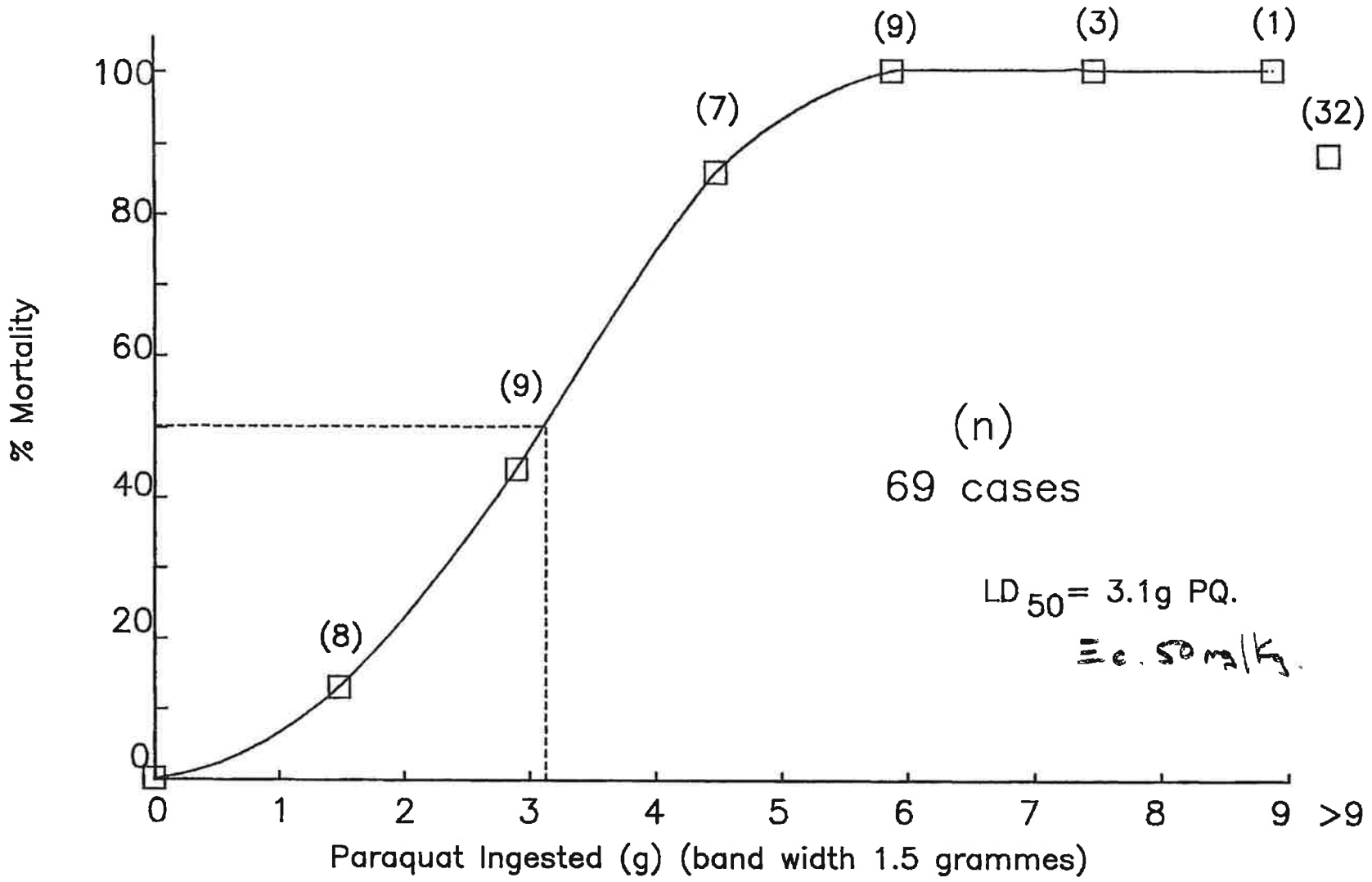


Fig 2.

JAPANESE HUMAN DATA (1986–7)

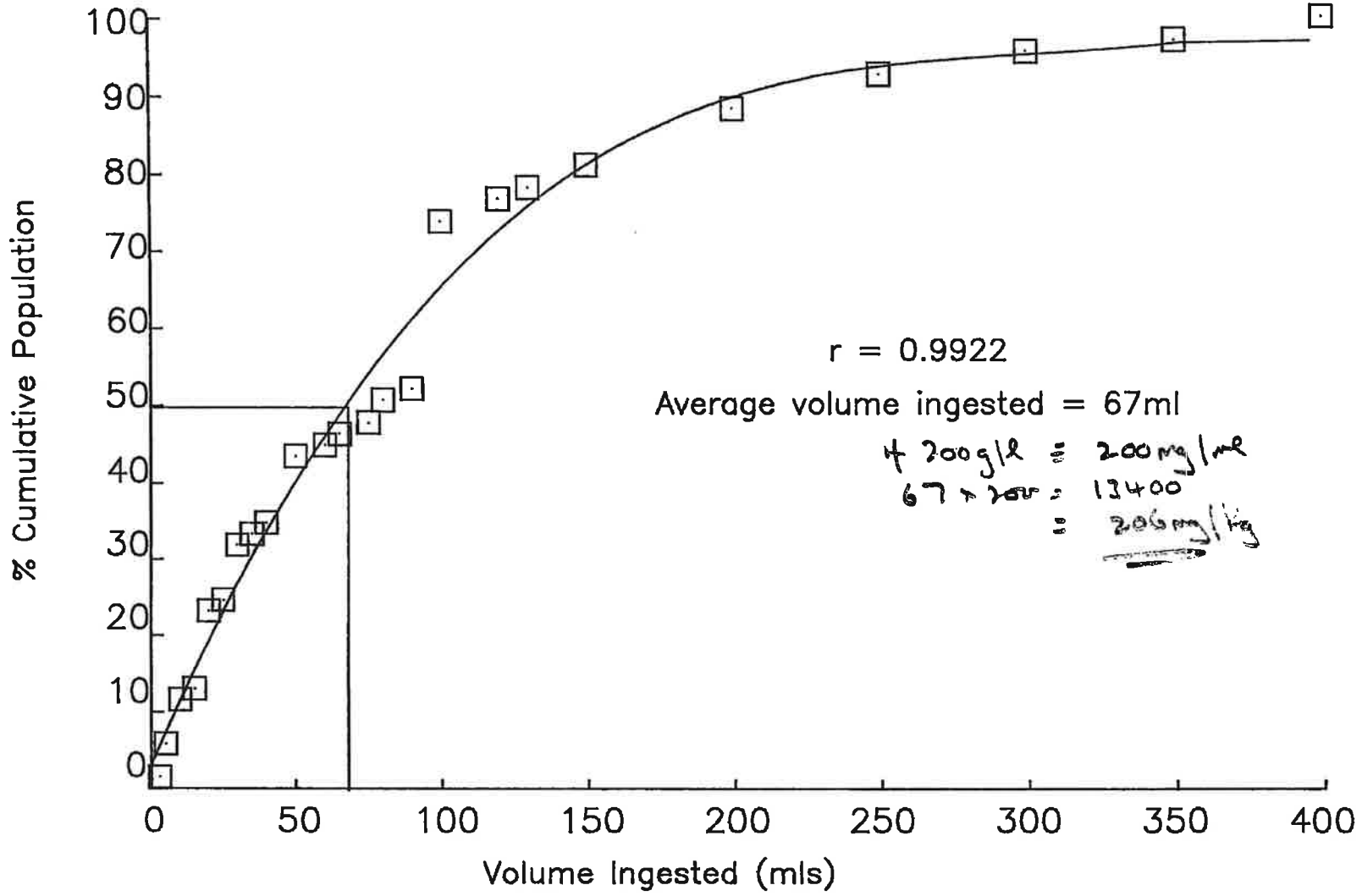


Fig 3.

JAPANESE HUMAN DATA (1986–7)

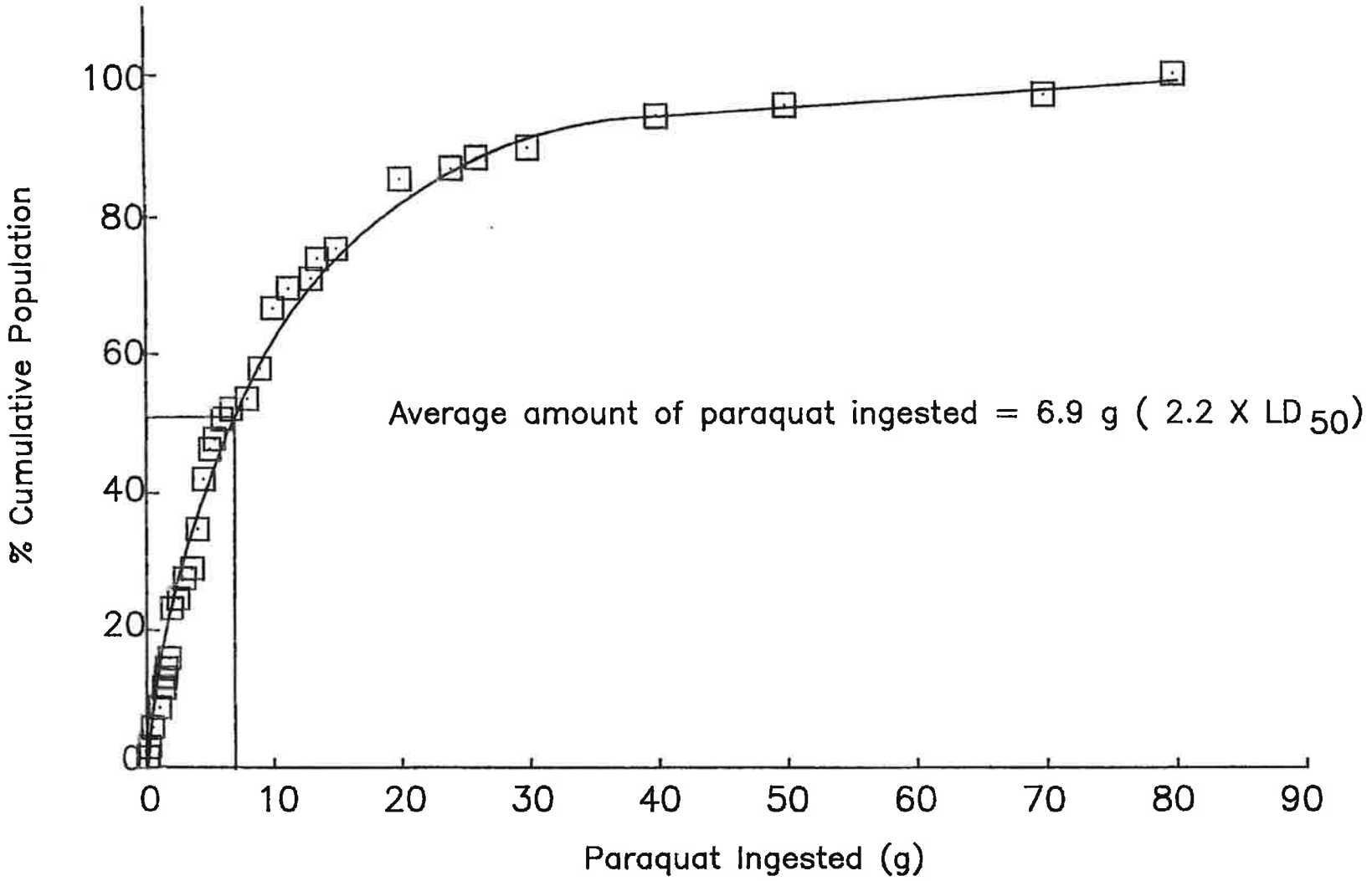
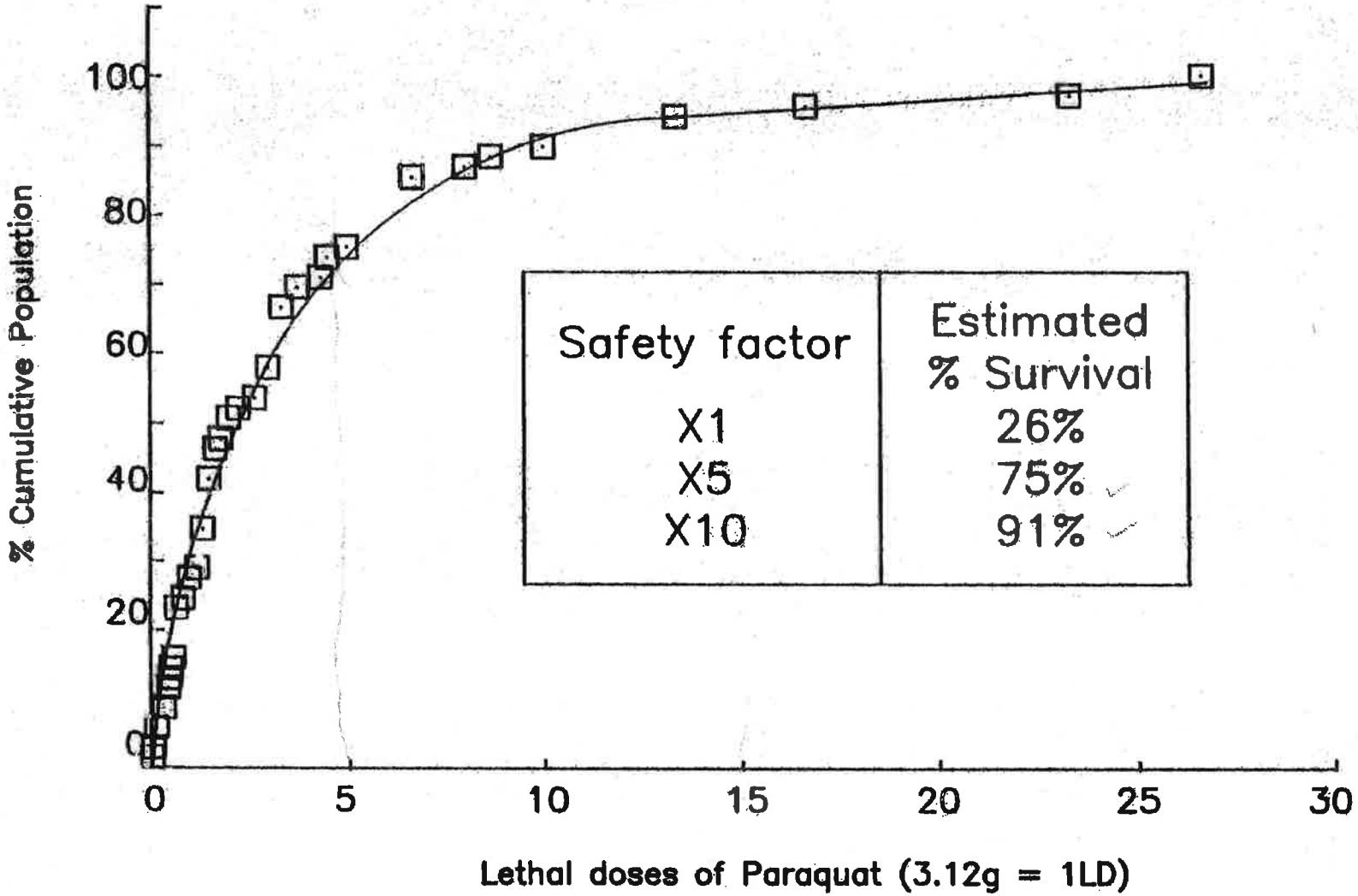


Fig. 4

JAPANESE HUMAN DATA (1986–7)



Safety factor	Estimated % Survival
X1	26%
X5	75%
X10	91%