

AGENDA ITEM 3 : PARAQUAT ALTERNATIVE FORMULATIONS

- Progress/resources/strategy

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RECOMMENDATIONS FOR AGENDA ITEMS 3 AND 4

- 1 The 'Weedol-type' high strength solid formulations of paraquat and paraquat-diquat be accepted 'on the shelf' for introduction only after the approval of the Committee, subject to satisfactory adherence to the hygiene standard at Yalding. No further work is planned on this project.
- 2 The current development of an alternative 'flake' solid at Yalding be completed (hopefully by end 1Q 1988) and the product assessed commercially in comparison with the above 'Weedol' formulations.
- 3 The current strategy opposite SDS be continued. A thorough review will be necessary in March 1988.
- 4 Development of a thickened formulation on an international basis be discontinued.
- 5 The target profile for the primary and secondary objectives for a multiple emulsion formulation described in Section 5.1 be approved.
- 6 Development of such formulations be pursued with all vigour in 1988 with the objective of achieving a development product by end-year. It is recognised that the achievement of the primary objective of this programme (viz a possible 'economic solution' to the poisoning problem) may not be achieved on this timeframe. It is recommended however that, if a candidate formulation is available by 2Q 88 which does not in all respects meet the requirements of this primary objective, this formulation is taken through to a state of commercial readiness with all speed by end-1988. Such a formulation will then be available as an extra candidate for the 'basket of options' strategy for alternative paraquat formulations.
- 7 Extra resource will be necessary to pursue such a programme without disturbing the existing exploratory resource targetted towards achieving the primary objective. Committee support is requested for the necessary increase in Jealott's Hill and CTL resource. Current thinking suggests a need for 2 extra technical officers for 6-12 months. Consideration is being given to inward secondment from the Paints business or ICI Americas. The TRC will endorse the final scheme proposed.
PSAC
- 8 Publication of the ICI multiple emulsion patents be completed by 13 January 1988 in order to secure ICI's rights in this field.
- 9 The current low level of resource on other research projects be maintained. During 1988 the emphasis of this work will be on the gut absorption programme at CTL.

Optimistic

2 BACKGROUND

2.1 Current liquid formulations

The current formulations of 'Gramoxone' containing 200gm ion per litre paraquat and using a 5-10% Synperonic NX and Nansa/Synprolam DBBS wetting system represent extremely attractive products in techno-commercial terms both to the farmer and to ICI.

- They are effective and robust biologically under the wide range of environmental conditions ruling in the 130+ countries in which the product is sold.
- They have good stability/dilution properties.
- They are easy and convenient to use at application rates normally between 1-5 litres per ha. This property contributes significantly to product safety in use for the farmer.
- The Nansa formulations tank mix well with other herbicides.
- They are cheap to manufacture. Variable formulation costs including wetters amount to £250/te ion, variable packing costs to £700/te ion. The current safening additives (blue, odour and emetic) add £150/te ion. In total therefore the formulation and packing adds £1100/te ion to the ai VPC of £3500/te ion.

2.2 The Paraquat Poisoning Problem

Experience over 25 years of sales indicates that, despite an oral LD50 to rat for 130mg/kg, the oral toxicity to humans is such that, for the 200gm ion/litre formulations above, the minimum lethal dose from ingestion is judged at 10ml of product. The LD50 dose level is put at 15-20ml (1 mouthful is approx. 40ml).

There are a number of key features associated with paraquat poisoning cases which have tended to attract particular attention from the media/regulators:-

- a) At low dose levels death is brought about through lung fibrosis and is usually prolonged and unpleasant.
- b) Whilst successful treatment methods have been developed (haemodialysis, haemoperfusion and Fuller's Earth) these all need to be administered very quickly to patients. In rural areas this is very difficult especially with suicide incidents.
- c) 95% plus of current incidents are believed to involve suicidal or parasuicidal intent. Median dose levels are therefore high (usually 50-100ml) in relation to the minimum lethal dose above. At these dose levels death occurs from multiple organ failure and is usually more rapid.
- d) 'Gramoxone' poisoning cases thus display only a 20% survival rate (from all causes) compared with a more normal 80% survival rate for other chemical poisoning cases.

The net result of these features has been the continuing presence over a long period of a strong media/regulatory lobby (often fuelled by deep concern within the medical profession) for the withdrawal of paraquat sales in many countries. Often the lobby has little appreciation of the agricultural benefits accruing from the usage of paraquat.

2.3 ICI's Response

From an early date ICI recognised its responsibilities to minimise the occurrence of paraquat poisonings from genuinely accidental causes (eg decanting incidents). Safening additives were introduced into the 'Gramoxone' formulation from the mid 1970's : a colour (blue) and an odour (pyridine bases) as alerting agents to prevent accidental ingestion, and an emetic (PP796) to reduce the effective dose ingested. Where all three have been introduced and where product availability have been restricted, true accidents have been very much reduced or even eliminated (eg UK). There is a problem here of identification - regularly suicides are classified as accidents for religious/cultural reasons.

Despite the improvement brought about for accidents, fatalities from suicidal ingestion have continued at high levels and have in some instances grown as product usage and/or media publicity have increased (eg Japan and Malaysia). Whilst PP796 has proved an effective emetic in humans and has beneficial medical effect in cases involving 'marginal' doses (especially with 'Weedol'), it has not had any significant impact on survival rates at suicide dose levels.

ICI has always seen a firm distinction between its responsibilities for preventing genuine accidents and its attitude to suicidal abuse of paraquat which originates as a social problem and which will not be solved by the withdrawal of paraquat or otherwise. Our fundamental responsibility is to provide a product which is safe for use by the farmer, as directed on the label and to the operator during manufacture. Furthermore this responsibility to the farmer and operator should not be compromised by changes designed to reduce suicidal abuse of the product. Regulators/media have not however always seen the distinction in the same terms as ICI. As a result the lobby against paraquat withdrawal has not diminished. Demands continue to be made either for product withdrawal or for a change to 'safer' formulations in response to high levels of suicides. Japan, Malaysia and France are recent examples. The German lobby against paraquat started out for this reason - only later did it change to soil persistence.

ICI has continued to counter such lobbies with all necessary resource and efforts. Nevertheless in business terms it must be recognised that recent regulatory restrictions/withdrawals have led to a significant reduction in the Group profit generated by paraquat either through reduced sales or increased costs or both. (eg Japan, Germany, Switzerland, Egypt and now France from mid-1988).

3 Current Strategy for Alternative Formulations

ICI's actions in including the safening additives in the current liquid formulations are in-line with our responsibilities to minimise accidental fatalities with paraquat. We see no reason to change proactively from our current formulations. However the July 1985 Executive paper re-affirmed the need for a reactive strategy for formulation change given the existence of the 'business' problem brought about by suicidal/homicidal abuse of the product noted above. The Executive approved the strategy of developing alternative formulations to a commercial state 'on the shelf' in order to provide a 'basket of options' to offer to Regions/Regulatory Affairs Section when faced with a paraquat regulatory crisis. The strategy recognised that regulators may take a different view of responsibilities for suicides and may not always look for solutions to their problems which appear logical to ICI. However it also recognises that none of the alternative formulations currently available offer an economically-acceptable solution to the suicide problem either to ICI or to the farmer for the following reasons:-

- a) There are no alternative formulations available which significantly reduce ai toxicity per se. Suicidal abuse of the product will not be eliminated.
- b) The current liquid formulation would need to be diluted at least 5x (giving a minimum lethal dose of 50ml ie greater than 1 mouthful) to produce any measurable increase in the survival rate (the current feedback from 'Preeglox' in Japan supports this view). At this dilution level, formulation and packing costs would be increased by £2600/te ion and product usage by farmers would reduce significantly because of bulk inconvenience/higher prices.
- c) A solid formulation does act as an effective alerting agent against accidents and may lead to reduced dose levels in suicide cases. However ICI's experience with 'Weedol' clearly indicates that solids are widely used for suicidal ingestion. The 'Weedol-type' formulations available show poor dilution properties and are prohibitively expensive in fixed capital (£6m per 1000 te ion) and variable cost penalties. (£1300/te ion).
- d) The introduction of either formulation b) and c) on a global basis would destroy Group profit from paraquat.
- e) The addition of diquat in a mixture with paraquat will help to reduce oral toxicity and thus increase the minimum lethal dose for a given content of bipyridyl ion. The increase will be modest. Diquat is more expensive to manufacture than paraquat (£1000/te ion VPC) and is less effective on grass weeds. The introduction of paraquat-diquat mixtures has however provided another major benefit. The change of product trade name from 'Gramoxone' to 'Preeglox' in Japan has led to a reduction in the number of suicide incidents and thus fatalities, even though survival rate may be only marginally reduced.

For the above reasons the strategy foresaw that alternative formulations would only be offered to regulatory authorities as an alternative to product withdrawal. This process is co-ordinated, overseen and approved by P-S-A-C.

During late 1985 the workgroup structure for paraquat defence activities was revamped and projects dealing with alternative formulations managed through two workgroups.

4 FORMULATION DEVELOPMENT WORKGROUP (P J BRAMLEY)

4.1 Solids

Development effort at FDQA Yalding since late 1985 has been concentrated on producing a solid formulation of paraquat with the following key objectives:-

- rapid dilution time
- good sprayability/biological performance
- low friability thus obviating the need for soluble sachets
- a total bipyridyl content as close to 20% as possible but no higher
- requirements for formulation/packing which are compatible with ICI's existing facilities for paraquat round the world

Work has centred on three technology options:

- the magnesium sulphate 'Weedol-type' granule
- the Kelco matrix technology
- the SDS gelling solid

4.1.1 Weedol-type granules

Starting from a high strength concentrate of 400gm ion/litre FD&QA have developed two 'high strength' formulations suitable for use in agriculture:-

- 15% paraquat
- 8% paraquat + 4% diquat

These are the maximum concentrations of bipyridyl possible with this technology. Both formulations have been put through a SOP testing programme outlined in Appendix 1 including a plant trial at Yalding. The friability properties are such that it is not considered necessary to utilise closed soluble packs. The formulations contain Synprolam and Synperonic wetter, blue stench and emetic. Biologically they match the current 'Gramoxone' liquid. However they have three important drawbacks:-

- dilution time is 45 sec
- the Group VPC penalty is high (£700/te ion bulk raw materials plus £600/te ion dilution in the case of straight paraquat)
- the fixed capital cost penalty is high. Up to 40 te ion of these formulations (say 600 te product) could be made on the existing 'Weedol' plant at Yalding following minor modifications (cost £0.2m lead time 12 months). Such quantities could enable a market launch to be undertaken. Higher tonnages imply very high new fixed capital requirements ie - approx £6m per 1000 te ion on a brown field site.

An additional complication with these formulations has arisen following the proposal to reduce the hygiene standard for paraquat and concern that the 'Weedol' plant at Yalding would not adhere to that standard. The proposal was not in the event accepted but it was considered necessary to investigate in more detail both the amount of respirable material in the 'Weedol' plant and the epidemiology of the health of the workforce. Onplant trials are being conducted during 4Q 1987.

4.1.2 The Kelco Matrix Technology

The inclusion of this alginate matrix in solid paraquat formulations proved prohibitively expensive. Co-operation with Kelco ceased in September 1986. However work at FD&QA Yalding highlighted the prospect of using the Kelco-type drying process without the inclusion of their expensive matrix!

A flake-type solid has thus been developed to a 20% strength on the lab scale using a drum drier and a patent filed. The product is non-dusty, dissolves in only 15-30 seconds and storage is good. VPC penalties are expected in the range £500-1000/te ion for raw materials. Additionally this technology offers the prospect of reduced fixed capital requirements compared with the 'Weedol'-type depending on the exact needs for dust containment. A pilot plant trial at Yalding is planned for 1Q 1988 to resolve this issue once compliance with the hygiene standard has been resolved. Detailed economic, toxicological and biological comparisons with the 'Weedol'-type will follow if this is successful.

4.1.3 SDS Gelling Technology

Up to a few days ago it seemed that this 2 year old project was failing for technical reasons. This may have turned around following a new initiative by SDS.

The events of the past few months can be summarised:

- early in 1987 in meetings in Tokyo the available formulations were rejected technically. ICI considered dustiness unacceptable (we set the standard of "no worse than Weedol"). We agreed that the spray properties were probably acceptable, but expressed continuing concern that the spray had to be prepared in a certain way to avoid lump formation. At the meeting we also introduced, for the first time, the thought that the gel-forming characteristics were not sufficient to deter suicide attempts significantly.

Two objectives were set, and declared by ICI to be "not negotiable":

- a) Any new formulation must be simple and safe to use. Liquid formulations meet these criteria, and there must be no lessening of these standards with a new formulation. This point has been emphasised repeatedly.

b) The new formulation must offer a substantial reduction in suicides compared with "Preglox".

and

c) A 'relative' point, not discussed in detail, referred to commercial viability.

d) From early 1987 SDS agreed that all assessments will be restricted to the Japanese market.

SDS responded 2-3 months later with news of a formulation which satisfied the dustiness standards. ICI answered that the gel formation data supplied by SDS indicated weak properties, and referred SDS to objective (b) above.

Meanwhile, tests by CTL had confirmed that the intrinsic acute toxicity of the SDS formulations was only marginally better than that of 'Gramoxone'. L Smith and R Birtley visited SDS and convinced them that the formulation offered no significant improvement in toxicity, and insufficient deterrent to would-be suicides. SDS withdrew samples and support from Professors Naito/Yamashito of Tskuba University. Naito gave a paper in Hungary, but was prevented by SDS from demonstrating the formulation. The paper apparently raised little interest. There has been no further contact between SDS and Naito. SDS made no further contact with ICI (Fernhurst), until they sent a message requesting a meeting at Brighton.

At this meeting, on 16 November, SDS reviewed the situation as outlined above. They said they had been impressed by ICI/CTL comments on the weak gel-forming properties, and the fact that a drinkable preparation could be made by diluting the granules with water in anything more than a 5:1 ratio. They agreed that this was not adequate.

SDS set a new technical objective of a formulation which remains as a gel at up to 15:1 dilution with water. They produced samples of a new 20% paraquat formulation and supporting data (see Appendix 2), and photographs which indicate they have achieved this, while retaining satisfactory dust and sprayability characteristics (when diluted at 200 l with water the normal rate in Japan where high volume sprayers are used. ICI indicated that spray dilutions down to 40:1 were normal outside Japan, so these formulations had no chance of being acceptable to farmers elsewhere.

ICI agreed to carry out a series of tests, and report by early April 1988. A further, considered response will then be necessary to SDS taking into account the technical assessment of the new samples, the situation then ruling with 'Preglox' in Japan and the position with ICI's own solid formulations.

4.2 Thickened Formulations

4.2.1 France

For some years the French authorities have been threatening to activate the arrêté restricting paraquat liquid formulations to 40 gm ion per litre maximum ai content because of concerns over poisoning fatalities. Sopra estimate the cost penalty of such a move at £5000/te ion including local transport. In response to this threat Sopra and Jealott's Hill have developed thickened formulations based on xanthan gum and silica containing higher concentrations of paraquat and paraquat/diquat. The original goals of this research were seen as:-

- maximum 100 gm ion paraquat content (set by the authorities)
- 8-10x increase in viscosity of liquid formulations
- extremely unattractive 'duck-shit' appearance

This work has now been completed. In the event it has only proved possible to produce such formulations as 100gm ion/litre paraquat and 100gm ion paraquat plus 50gm diquat with a 5x increase in viscosity and a less 'unattractive' appearance. Nevertheless the French authorities have confirmed their acceptance of such col-type formulations as being distinct from liquids. The relevant studies on biology (Sopra field testing), storage stability/dilution and sprayability properties and toxicology have been undertaken and a registration dossier submitted. Market launch is expected in mid-1988. The Group VPC penalty associated with these formulations is £2000/te ion including local transport. The authorities are however proposing to monitor the progress of paraquat poisonings over an initial 3 year period. In this situation it is recommended that Sopra instigate a tradename change for both their new formulations - particularly in the French West Indies - to avoid association with 'Gramoxone'. The launch of 'Preeglox' in Japan provides evidence in support of this strategy.

4.2.2 International Formulation

During 1986 work was targetted at achieving thickened formulations of similar viscosity and unattractive appearance for use internationally. Once again it only proved possible to achieve a stable/sprayable formulation with a 5x viscosity increase and a reduction in unattractiveness (a 200gm ion paraquat content was achieved). Regional support and need for such a formulation was reviewed in May 1987. Because the original targets could not be achieved this work was terminated from mid-1987 and formulation resource switched to the more profitable multiple emulsion project.

5 **MULTIPLE EMULSION FORMULATION**
(W D McCLELLAN/L L SMITH/H SWAINE/P J BRAMLEY)

5.1 Objectives

This project has two main objectives:-

5.1.1 The primary objective is to develop a formulation which will maintain existing registrations for paraquat through producing a significant increase in the survival rate from poisonings and thus a longer term reduction in the number of poisoning incidents from whatever cause without incurring an excessive cost penalty to the business or reducing product effectiveness/convenience/safety for the bona-fide farmer in the field. Such an 'economic solution' to the business problem outlined above would then be available as part of the current reactive strategy to paraquat regulatory crises or for consideration as the basis of a pro-active strategy for formulation change. In order to achieve this objective the following target profile has been agreed for the multiple emulsion formulation:-

a) Toxicity/Safety in use

- A minimum 10x reduction in the formulation toxicity of 'Gramoxone' which would imply a minimum lethal dose not less than 100ml. Whilst suicide incidents will still occur in this situation, a significant increase in survival rate should be achieved towards the 70/80% achieved with other ag chem products (including 'Weedol').
- inclusion of at least one alerting agent (colour) and an emetic in the formulation
- sufficient robustness/simplicity in use to maintain the current safety-in-use levels associated with 'Gramoxone'.

b) Economic

- A formulation and packing VPC penalty to ICI less than £1000/te ion.
- TLFT? Compatability with existing formulation facilities both at the international sites and at local facilities overseas. Any fixed capital penalty would then be minor (say '£0.1m per 1000 te ion).

c) Biological

- ✓ - Field herbicidal activity not less than 90% that of the 'Gramoxone' with-wetter formulation.

d) Formulation/Packing

- Never? Stability/storage properties close to those of 'Gramoxone' under the wide range of environmental conditions in which the product would be used worldwide.
- Tank-mix compatibility with other herbicides.
- Inclusion of built-in wetter if needed to achieve c).
- Sold in one container as with 'Gramoxone' (ie no need for twin or unimix pack) to maintain the convenience/simplicity in use for the farmer noted under a).

5.1.2 It is recognised that the research programme may result in formulations which do not meet all these targets at once. Such formulations would however be available to meet a secondary objective of providing further candidates for the 'basket of options' in the current reactive strategy outlined previously. The target profile for such formulations is less demanding than for objective 1 - in particular formulations generating an increase in minimum lethal dose of 5x would provide some increase in survival rate and could be a useful alternative for regulatory authorities.

Two likely candidate formulations are:

- a) One which is only stable if the wetter necessary to achieve good biological results is added after dilution in the spray tank and
- b) One which requires a specific chemical stimulus to revive biological activity from a reduced toxicity paraquat formulation

Alternative a) is considered acceptable as a fall-back position in the 'basket of options' although sales volumes/farmer usage would be significantly reduced if introduced in less sophisticated markets. The product would inevitably gain a reputation for less robust performance.

Alternative b) would require a twin or unimix pack for effective marketing to farmers. This is considered unlikely to increase the survival rate from suicidal ingestion but may appeal to regulators as another measure designed to counter accidental poisonings. The safety-in-use aspects of such packaging would need to be carefully considered.

5.2 Resourcing Strategy

In pursuing evaluation of formulations to meet these objectives it was agreed through the Jealott's Hill TRC in 1986 that, because of the size of the paraquat business and because of the regulatory pressures on the product, once candidate formulations to meet these targets were identified technical resource would be diverted to this project as intensively as possible consistent with good scientific practice, committed to a thorough evaluation of the likely chance of technical success in a short timescale but then reduced as necessary if success proved elusive. A summary of current resource levels devoted to this project will be presented at the meeting.

5.3 Principles

The concept of preparing multiple emulsion formulations of paraquat which are intrinsically less orally toxic than the 'Gramoxone' aqueous solution range has been actively pursued over the last 12 months. The work has been directed by Dr Th F Tadros supported by 3 Blue Book chemists at Jealott's Hill.

The multiple emulsions prepared to date have been water-in-oil-in-water (W/O/W) formulations, see figure 1. Aqueous paraquat concentrate (360 g/l) is emulsified into an oil using appropriate polymeric emulsifiers. This water in oil emulsion is then itself emulsified into a sodium chloride aqueous solution using a second polymeric emulsifier system. The concentration of sodium chloride in the 'outer' aqueous phase is selected to osmotically balance the paraquat dication concentration in the primary emulsion. The overall concentration of paraquat dication in the formulation is 100 g/l. The 'liquid membranes' encapsulating the paraquat are intended to survive oral ingestion and thereby reduce toxicity. On dilution into the spray tank it is anticipated that osmotic pressure will rupture the membranes. In addition the multiple emulsion structure is thought to be unlikely to survive drying down on the leaf surface and hence bioefficacy should be retained.

5.4 Progress to Date

5.4.1 Toxicology

A strategy for evaluating the animal toxicology and phytotoxicity has been developed between PPD and CTL. Formulations are first tested in rats to assess acute toxicity. Parallel studies are in Weed Science at PPD in order to test sprayability and herbic activity. Following these assessments, more detailed studies in dog are carried out at CTL.

Primary Evaluation in the Rat

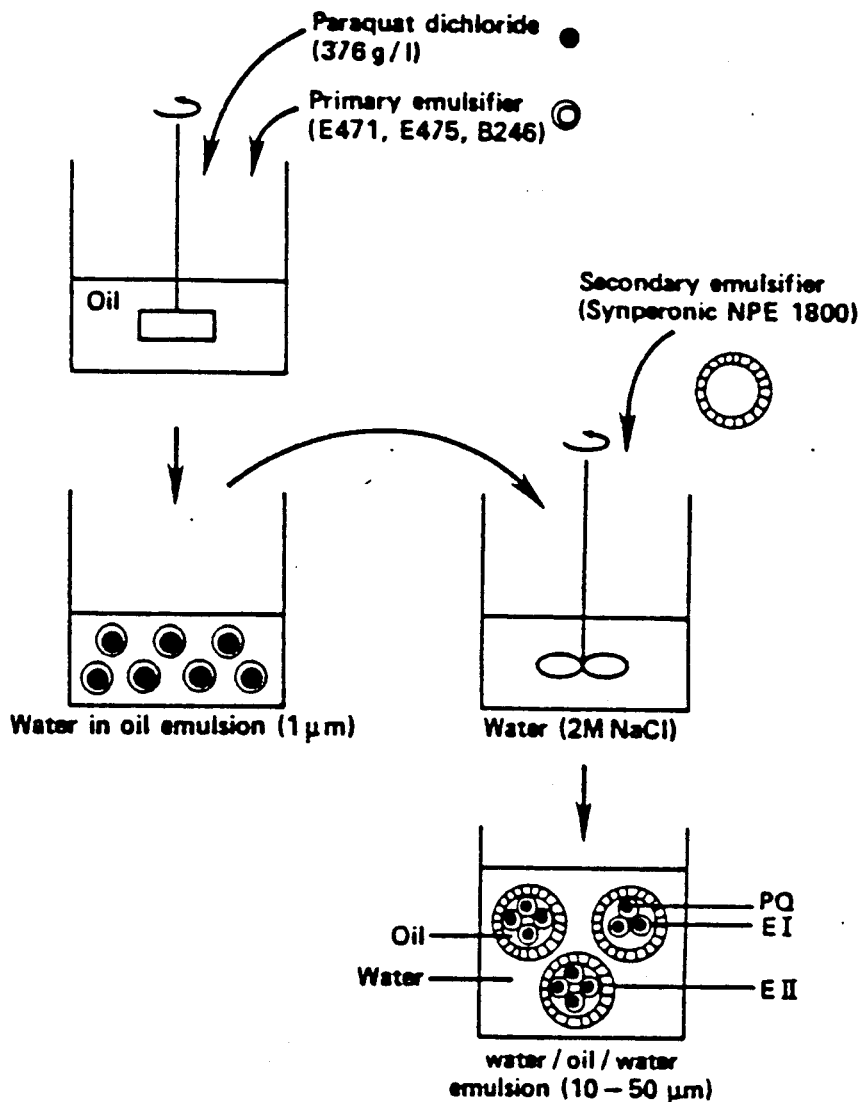
All the multiple emulsion formulations of paraquat have contain 100g/l of paraquat ion. Five adult male rats are gavaged with this concentrate following an overnight fast. The standard dose level is 200mg PQ ion/kg which is about twice the LD50 for conventional paraquat formulations such as 'Gramoxone'. Animal monitored for signs of toxicity for 10 days. A good correlation has been observed with the stability and leakage of paraquat from the formulation and the toxicological outcome. Between February and September 1987 we have evaluated more than 80 different emulsion formulations which have included various control emulsions and paraquat standards. Of these, about 10 have shown no acute toxic effects in rats at the paraquat LD50 x 2 dose level. The composition of the emulsion formulation is multivariable. Each constituent is being systematically evaluated in an attempt to optimize the safety and sprayability properties of the multiple emulsion formulation.

This strategy needs refining & tightening up in methodology

?

FIGURE 1

PREPARATION OF MULTIPLE EMULSIONS



Multiple emulsion formulations of paraquat are based on containing paraquat within a water/oil/water emulsion. They are made by mixing a primary emulsifier with a paraquat concentrate in an oil. This mixture then undergoes a secondary mix with another emulsifier to produce droplets which are 10-50 μ m in size. On dilution, the herbicide is released by osmotic disruption of the droplets.

Secondary Evaluation in the Dog

As in our rat studies, the neat paraquat concentrate is administered by gavage following an overnight fast. Both clinical signs are monitored and blood samples taken. Plasma paraquat is measured by either radioimmunoassay or HPLC on samples taken over the first 24 hours after dosing. All control animals receive sub-lethal doses of paraquat (8mg/kg) as 'Gramoxone'. Extensive studies with the same dogs have shown intra-and-inter-animal variation to be low with respect to plasma paraquat area-under-curve (AUC) data. Using this data-base, and commencing at the same dose level (8mg/kg) with emulsion formulations, direct comparisons of plasma paraquat levels have been made with 'Gramoxone'. Only those formulations which show a significant reduction in absorption of paraquat into the bloodstream at this low dose level are repeated at higher doses on subsequent occasions.

To date, we have assessed 7 emulsion formulations in the dog and by progressing the dose level at small intervals from 8, 16, 32, 48, 64 to 80mg/kg, we have demonstrated different degrees of safening between the different emulsions. For instance, our most promising formulation in terms of toxicology comprises the primary emulsifier B246 (a synthetic co-polymer), diesel oil and NPE 1800 (secondary emulsifier). This formulation of paraquat is non-toxic to dogs at 64mg/kg (Figure 2). Plasma AUC values are comparable to an 8mg/kg dose of 'Gramoxone' and animals showed no signs of toxicity. This eight-fold safening factor is put into perspective when compared with contemporary toxicity data generated this year at Inveresk Research International which gives an LD50 of 12mg/kg in the dog for conventional commercial formulations of the herbicide. Other closely related emulsions where the oil phase contained soya oil in place of diesel oil have demonstrated only about a 2-3 fold safety factor when the plasma paraquat AUC is compared with 'Gramoxone' (Figure 2).

Other formulations are currently under investigation in rat and dog studies. The majority of these are based on the primary emulsifier B246 and diesel oil, but with a view to producing a more sprayable product without hopefully compromising the reduction in toxicity already achieved.

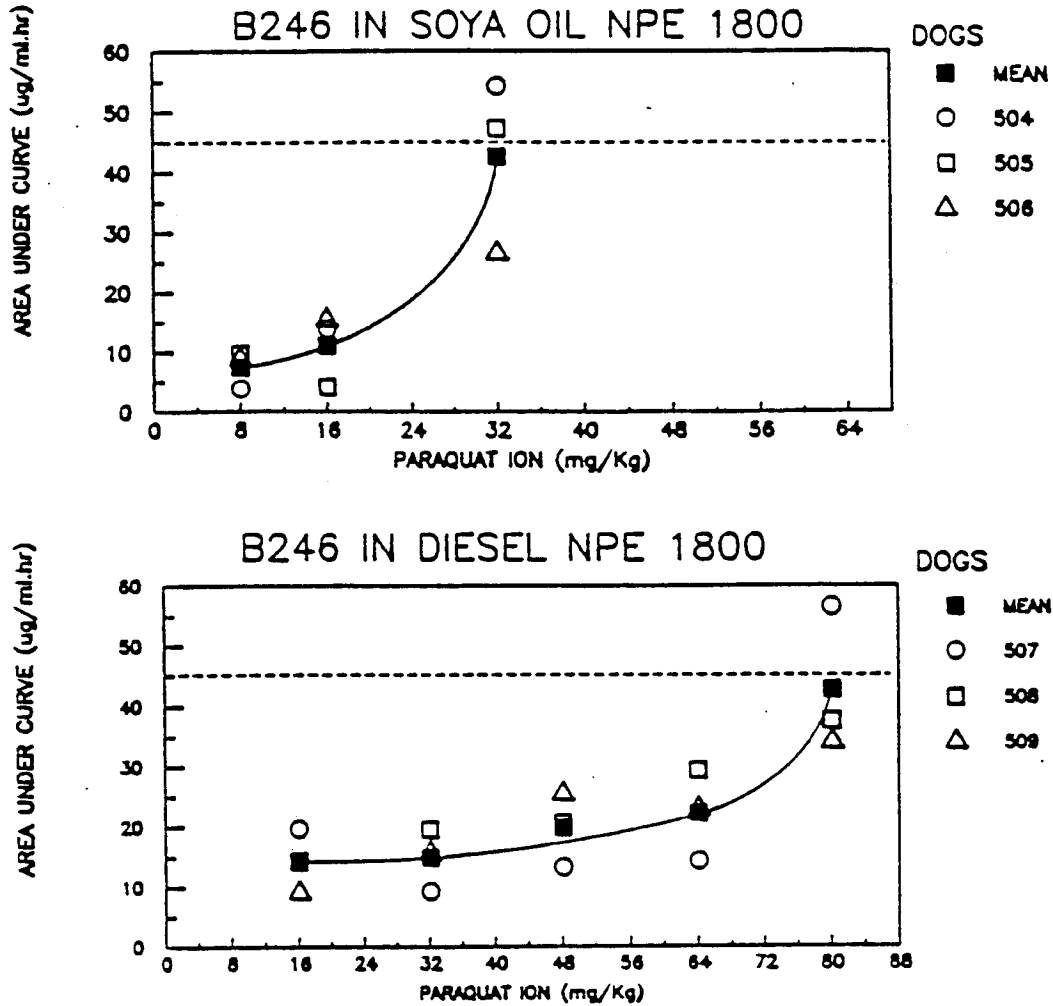
5.4.2 Formulation Chemistry

Many variations to the basic theme have been investigated. As noted above, to date the best toxicology results in both rat and dog have been obtained with a formulation based on:-

primary emulsion system	- B246 (ICI Speciality Chemicals)
oil phase	- diesel oil
secondary emulsion system	- NPE1800 (ICI Speciality Chemicals)
aqueous phase	- 2 M NaCl solution

FIGURE 2

RELATIONSHIP BETWEEN AREA UNDER CURVE AND DOSE LEVELS
WITH TWO FORMULATIONS OF B246



Effect of increasing dose levels of paraquat and the plasma area-under-curve (AUC) in the dog. Formulations containing B246 and NPE 1800 as the emulsifiers show different rates of paraquat absorption when the nature of the oil is changed. Soya oil formulations (upper panel) were more toxic than diesel formulations (lower panel). Each dose level represents three observations in the same animal with one month intervals between successive doses. The dotted line represents the AUC value below which all animals have survived.

Formulations have also been prepared using isoparaffinic oil and these too show improved toxicity but to a lesser degree than diesel oil based systems.

Refinements to the basic theme are being systematically evaluated. Cross linking polymers are being investigated for their potential to further 'stiffen' the outer liquid membrane. The capacity for inclusion of surfactants to enhance bioefficacy and the scope for introduction of colourants and the emetic are among the themes being followed.

Surely this is a premature diversion.

The concept has now been demonstrated to be sound in terms of toxicology. The next stage is to develop formulations which meet our usual criteria for shelf-life, dispersibility and bioefficacy. However these objectives are likely to be highly demanding technically and will require thorough investigation. Problems have already been encountered with the dispersion properties of multiple emulsions. Reproducibility of precise specification has also been identified as a putative difficulty.

WHITE WASH!

5.4.3 Patents

A patent covering the above formulation types was filed 13.1.87. Publication must therefore be completed by 13.1.88 to secure our rights to this property. If successful the patent will be issued mid year 1988. The strong recommendation from Formulation and Patents Sections is that the patent should be completed. It would be argued that any indication to Registration Authorities of 'safer' formulation of paraquat being available to ICI could compromise our position. However, the need to protect this area from others known to be active in the field is seen as an overwhelming case for patent completion.

5.4.4 Biology

The biology studies with the multiple emulsions have been evaluating the lead formulations in the glasshouse and the field. The objective of these studies has been to ensure that the formulation meets the following criteria:-

- A Efficacy on key weed species '90% of 'Gramoxone' efficacy in 90% of situations;
- B Dispersibility and Sprayability of the formulation is acceptable.

The formulations tested to date have demonstrated varying levels of efficacy with some of the latest tested having activity comparable to 'Gramoxone'. This indicates that efficacy levels similar to 'Gramoxone' can be obtained.

The major problem with these new formulations is that they do not have acceptable dispersability in the spray tank and are not sprayable due to filter blockage.

If these criteria can be met with improved formulation during the next 6 months, a field programme to test these formulations is anticipated to begin in mid 88. The initial phases of the field programme will be done only on ICI research farms in selected ~~formulations~~. ~~The Paraquat Research Group must monitor and oversee~~ the programme to ensure the confidentiality of these novel formulations.

5.4.5 Economic

Appendix 3 summarises a preliminary costing undertaken for the B246/diesel oil/NPE 1800 emulsion. In total a raw material VPC penalty of £530/te ion is incurred cf 'Gramoxone' if stench is omitted and extra wetter is not needed plus a dilution/packing cost penalty of £350/te ion. The major element is the raw material cost is B246 supplied by ICI Speciality Chemicals at £565/te ion. Preliminary discussions have been held with that business around their transfer price quote. It is expected that further price reductions (10-20%) will be possible if significant offtake develops. It may however be necessary to include a specialist wetter system as with 'Gramoxone' which would increase the Groups VPC penalty to £1110/te ion.

Further definition of the formulation is required before estimates can be made of any extra formulation/packing process costs (ie labour) and new fixed capital at ICI's formulation sites. It is however anticipated that these will be modest.

5.5 Future Work and Resources

To date the research on multiple emulsions has produced formulations which have made a good start in achieving the targets listed for the primary objective in 5.1.1. They are:-

- patentable
- achieve up to an 8x fold reduction in the intrinsic toxicity of the formulation in dog, which combined with the 2x dilution to 100g m ion paraquat achieves the key toxicity target of a 10x reduction with some degree of safety margin.
- likely to involve a Group VPC penalty close to £1000/te ion
- likely to be compatible with current 'Gramoxone' packaging and with ICI's formulation/packing facilities.

However serious problems have been encountered in achieving the biological and formulation targets largely because of flocculation after dilution in the spray tank and storage problems. Such a situation suggests the need for intensive use of specialist formulation research resource directed at the identified problem. Jealott's Hill management are reviewing the options available and discussions are being held with ICI Americas and Paints Division to ascertain whether an inward short term secondment would be possible.

This is only one of two problems - the second is reproducibility - which may negate some of earlier (optimistic) results!

It is judged very likely however that in the short term it will only be possible to meet the biological and formulation targets by compromising on the toxicity and economic targets for the primary objective. The workgroup believes that project and research momentum would be considerably enhanced if such a candidate formulation was taken through to a state of commercial readiness by the end of 1988 if possible. From a business view point, this formulation would then be available as another alternative in the 'basket of options' strategy for potentially-crisis markets like Japan or France.

✓
also
to put
pressure
on
TFT
?

It would not however be possible with current resourcing levels to undertake such development work in 1988 and continue the exploratory research work necessary to overcome the serious problems encountered in meeting the primary objective. A delay to this latter activity and thus a step-wise utilisation of Jealott's Hill formulation resource is not considered appropriate in view of the increasing pressures on paraquat registrations.

P-S-A-C support is therefore requested for the current resource increases being sought by Jealott's Hill management and any consequent increase in CTL resource. The final solution will be endorsed by the TRC process. Currently it is envisaged that such resource will amount to 2 man years at Jealott's Hill and up to 1.5 man years at CTL.

6 DR UKAI AND CO-WORKERS

In early 1987 Dr Ukai and workers at Gifu College in Japan developed the use of dextran sulphate both as an effective treatment for paraquat poisonings and as a pre-mix with paraquat formulations to reduce oral toxicity. ICI Japan arranged to take over the patenting of these inventions. An agreement is being discussed for compensation to Ukai in the event of commercialisation. In fact CTL believe that as a treatment dextran sulphate will suffer the same problems as those associated with Fuller's Earth. ICI would not wish to commercialise such an application. As a formulation premix it has not proved possible to achieve both biological efficacy and toxicity reduction. ICI will not therefore commercialise this usage. ICI Japan have contributed £4000 to Dr Ukai in 1987.

This research programme has recently thrown up new possibilities for a formulation pre-mix based on glucose, sucrose and polyvinyl-alcohol sulphates. ICI has agreed to supply further modest support in 1988 (£4000) as an alternative research line in this difficult area. Regular visits will be made by ICI UK staff to ensure Dr Ukai's programme is monitored and he understands ICI's objectives.

STANDARD TESTS FOR NEW PARAQUAT SOLID FORMULATIONS

- 1 Paraquat content PPSM 192A
- 2 Dispersion time
- 3 Wet sieving retention test PPSM 121B
- 4 Friability test PPSM 40B
- 5 Bulk and packing densities PPSM 119C.
- 6 Hygroscopicity test and flowability PPSM 47.
- 7 Biological glasshouse trials (species, Ga, Ca, Pi Ag, Av, Sm, Ll, St, 0-10 scale, 1,4 + 12 DAT).
- 8 Spray performance
 - Beaker tests
 - Knapsack tests

**Physical Properties of Newest Paraquat WDG
(Lot No. H-72342)**

① Paraquat Content

Paraquat ion	19.16%
Paraquat dichloride	26.46%

② Gelling Speed (dilution × 15)

32 seconds

③ Dispersion Time

27 seconds

④ Pass Test

500	297	250	210	(μm)
○	○	○	X	

⑤ Angle of Repose

 $\Theta = 43.2$ degrees

⑥ Bulk Density

0.3

⑦ Friability (% pass and retained)

pass through 250 μm sieve	retained on 125 μm sieve	retained on 63 μm sieve	pass through 63 μm sieve
0.287	0.276	0.011	nil

⑧ Spray Test (50 g of Paraquat WDG/10 l of water)

During spraying	No blockage
Lumps	No lumps
Lance filter	Below 1% covered with gelatinous deposit

(This test was conducted using an ICI blue Polijet nozzle with lance filter in order to compare with the ICI data.)

Sprayer type	ML-15S (Yokohama Ueki K.K.)
capacity	15 l
pressure	1 bar
lance filter	400 μm

⑨ Hygroscopicity

This test has been started now. The water content of Paraquat WDG will be measured until its equilibrium state.

⑩ Storage Test

This test has been started and Paraquat WDG will be stored for 3 months at 40°C.

APPENDIX 3

PRELIMINARY COSTING OF MULTIPLE EMULSION FORMULATION

100gm ion paraquat per litre

<u>Ingredient</u>	<u>gm per litre formulate</u>	<u>Price of ingredient £</u>	<u>Price/ litre formulate £</u>	<u>£/te ion</u>
Diesel	150	7p per lt	0.01	105
B246	25	£2.25/kg	0.056	565
Synperonic NPE 1800	5		0.005	50
CMC	10		0.003	30
Sodium chloride	20	10p	0.002	20
TOTAL FORMULATION RAW MATERIALS				770
EXTRA PACKING/DISTRIBUTION COSTS cf GRAMOXONE 200 GM ION/LITRE				350
EXTRA COLOUR				+30
OMIT STENCH				-40
WETTER				-230
NET PENALTY (no wetter needed)				880
(wetter needed)				1110

NB Estimates of extra formulation/packing labour costs and fixed capital requirements are not yet possible. It is anticipated that they will be modest.