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ZENECA Agrochemicals

Yalding Technology Centre
Yalding, Nr Maidstone, Kent

Report Series

TMY0801C

Safer Paraquat - A Summary

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Date of Issue: 29 May 1996

Category

Company Secret

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ABSTRACT

Many attempts have been made within the Company in the last three decades to reduce the oral toxicity of paraquat formulations, in an attempt to decrease the incidences of accidental poisoning.

Some of this work has been reported in formal in-house documents; much exists only as raw data.

This document presents a brief summary of each of the approaches adopted, with relevant references, should a more detailed search be required. The report is divided into two main areas covering Liquid and Solid Formulations.

KEYWORDS
Paraquat
Emetic
Dye
Stenching Agent
Toxicity
Safening
Formulation

SUMMARY

Numerous attempts have been made in the last three decades to decrease the incidences of accidental paraquat poisoning by reducing the oral toxicity of paraquat formulations.

Approaches adopted were generally regarded as being global solutions, and ranged from the inclusion of alerting and safening agents in simple liquid formulations, to the investigation of more complex solid formulations.

Many of the attempts, particularly in the case of solid formulations, left unresolved technical issues, which, coupled with the major SHE and cost implications involved led to their being unacceptable as global solutions.

Several of the more viable options for liquid formulations eg addition of dye, stench and emetic have been adopted globally, while others such as the use of thickening agents are employed in specific markets such as France in response to demands from Regulatory Authorities.

SAFER PARAQUAT - A SUMMARY

CONTENTS

1 INTRODUCTION

Considerable effort has been expended in the last three decades in striving to reduce the oral toxicity of paraquat. Some of this work has been published in in-house reports; much remains formally undocumented.

This report attempts to summarise work in the area of safer paraquat formulations without aiming to be a comprehensive history of work in this field. It was initially embarked on as a learning exercise for the author, and is therefore meant only to be a guide document, listing references in order to enable a more detailed search to be attempted if necessary.

All the work described related to generating a global 'solution' ie formulations which needed to be suitable for sale in bulk and small packs, and for use in the full range of large scale and knapsack sprayers.

2 LIQUID FORMULATIONS

2.1 ADDITION OF COLOUR, STENCH, AND EMETIC

Knowles et al, Yalding, 1970's

Studies in the early 1970's into ways of minimising accidental ingestion of paraquat had recommended that stenching and colouring agents be incorporated into formulations. The choice of colour was to be restricted to blue or green as these were not foodstuff colours.

The initial programme of work concentrated on identifying suitable colouring agents in the absence of stench. Intensity of colour and storage stability data eventually narrowed down the choice to one pigment, Monastral Blue BNV.

A range of potential stenching agents, including pyridine bases, butyric acids, valeric acid, butylaldehyde and triethylamine were then screened. All caused flocculation of the pigment, although this was less marked in the case of pyridine bases. The problem was exacerbated by the presence of built-in-wetter systems.

Although water soluble dyes did not impart the same intensity of colour as the particulate dyes, they were less susceptible to compatibility problems and were therefore seen as a potential solution. A number were screened, and several suitable ones, including Patent Blue V identified.

Pyridine bases was chosen as the most suitable stenching agent, except for use in the USA where it did not at the time have EPA approved status. This led to the selection of valeric acid for use in US formulations; choice of level is thought to have been purely subjective.

Meanwhile, a number of potential emetic agents had been considered but discarded because of the very large amounts required for effect. However in 1976, PP796 was identified as a fast acting, powerful emetic, required only in small doses to be effective. An extensive testing programme followed, leading to the introduction of PP796 in paraquat formulations a few years later.

REFERENCES

REPORTS: AR2279B; AR2520B; AR2744C; TMY143B; BEP 190MR; PJ21/75/1C.

PATENTS: GB 1406881; GB 1507407; GB 1574600; GB 1570981; GB2116844; US 3920443; US 4046552; US 4075005; US 4160017.

2.2 THIXOTROPIC FORMULATIONS

Knowles et al, Yalding, early 1970's

One of the most common causes of accidental paraquat poisoning in the late 1960's/early 1970's, was the ingestion of Gramoxone which had been re-packaged in beverage bottles. Thixotropic gel formulations were therefore seen as one possible option to reduce this occurrence as they would be difficult to re-pack into a narrow-necked beverage bottle, and once in, would require vigorous shaking to be pourable again.

Additional criteria for an acceptable formulation were that it was readily pourable from the wide-necked sales pack after shaking, stable to storage and shear/gel cycling, and had satisfactory dilution properties. Low incremental cost and comparable biological activity were essential; safety targets were undefined.

The use of clays and cellulose derivatives, the most common thickening systems of the day, did not produce satisfactory rheology because of the high electrolyte content of the formulations. The then relatively new polysaccharide 'Kelzan' was found to be more tolerant to the presence of strong electrolyte, but gave variable results. This variability was eventually traced to differences in quality of paraquat batches .

Small amounts of borate ion, added as corrosion inhibitor to some batches of paraquat, acted as cross-linking agent and gave thixotropic gels with Kelzan. Not surprisingly, there was a direct relationship between borate and Kelzan concentration, and gel strength and pH. As expected, there was a trade-off between dispersibility and gel strength. The best compromise between gel strength at 25°C and dilution properties, was achieved in a formulation containing 0.4% w/w Kelzan and 140 ppm sodium metaborate tetrahydrate.

This formulation was designated YF6399, but caused concerns over the variation of gel strength with temperature - the product was only usable between 5°C and 30°C, the viscosities being unacceptable outside these limits. An additional problem was the sensitivity of effectiveness of cross-linking agent to paraquat quality. A further drawback was the high packaging and transport cost implications as a result of the requirement for large ullage

volumes in the sales packs. These problems collectively meant that the product was therefore never commercialised.

Unresolved issues included:

(i) The robustness of the formulation under a range of storage conditions.

(ii) Sprayability using a wide range of application equipment.

REFERENCES

REPORTS: AR2398B; AR2471C; AR 2488B; TMF 0778B; TMJ0737B; TMJ 0734B; TMY 0118B; TMY 122B; TMY 134A; TMY0145B; TMY 0147B.

PATENTS: GB1395502

2.3 THICKENED FORMULATIONS

2.3.1 Polymeric Systems

Knowles et al, Yalding, 1974 - 1975.

Because of the problems encountered with the thixotropic formulations, it was decided to attempt to produce thickened formulations that were not cross-linked. Such formulations were perceived as potentially having the right consistency to make swallowing difficult, as well as being more stable to temperature changes and easier to dilute. The formulation was to be coloured and stenched as further deterrents.

A range of polymers were evaluated as potential rheology modifiers. These belonged to three main classes:

(I) Polysaccharides - carrageenans, alginates, pectins, agar, galactomannans, and xanthan

(ii) Cellulosics - sodium carboxymethylcellulose and hydroxyethylcellulose

(iii) Synthetic hydrocolloids - polyvinyl pyrollidone, carboxyvinyl polymers and polyethylene oxides.

Carrageenans, alginates and pectins in the presence of calcium ions produced rigid indispersible gels, susceptible to syneresis, and were therefore unsuitable. Galactomannons were similarly unsuccessful, initially giving unacceptable rheological properties, with the gum being eventually precipitated out by salt.

The cellulosics and synthetic polymers did not impart adequate thickening.

The xanthan gums, Kelzan and Keltrol, which differ slightly in terms of purity, were evaluated. Keltrol gave a very small, albeit unacceptable degree of gelation to the formulation, even in the absence of cross-linking agent. Further investigations were therefore focused around Kelzan, which had previously been used with sodium metaborate to give thixotropic paraquat formulations (Section 3.2). Stenched, coloured, formulations with acceptable rheology were produced. However, these gave an insoluble "stringy" precipitate on dilution; furthermore, the properties were temperature dependant, particularly above pH 6.

These problems were thought to be caused by the presence of minute traces of metal ions in the paraquat concentrate. Although the ions responsible were never successfully identified at Yalding, a subsequent programme of work led to the identification of a possible solution through the use of anionic/nonionic surfactant blends.

Parallel work at Bernay led to the successful launch of Gramoxone Plus and R'Bix/Speeder, thickened formulations based on 100 g/l paraquat ion. The latter also contains 50 g/l diquat. Higher levels of emetic were incorporated into both formulations in the hope that this might result in improved safening.

A 200 g/l thickened formulation based on Kelzan was successfully developed at Yalding in the early 1990's, for Polish and Hungarian outlets.

REFERENCES

REPORTS: PJ21/75/1C; AR2616B

2.3.2 Surfactant Systems

Knowles et al, Yalding, 1974-1975, 1981.

Early toxicological studies had shown that paraquat uptake in dogs was greater in the case of built-in-wetter formulations, when compared with wetter-free Gramoxone. The prime cause was the presence of cationic surfactants, included to improve bioefficacy; these were preferred over other classes of surfactant because of their supposedly greater compatibility with paraquat.

A programme of work was undertaken to replace these cationic surfactants with a nonionic/anionic blend; this would not only reduce inherent toxicity, but by increasing the viscosity of the formulation, would make it more difficult to swallow. Formulations also had to be stenched and coloured.

The main criterion for success was to produce homogeneous formulations without compromising the bioefficacy of the formulation.

A large number of nonionic/anionic blends at various ratios were screened. Most were unsuitable because of the unacceptable storage and/or dilution properties of the formulation. The most promising candidates were subjected to bioefficacy and toxicology screens; although activity was equivalent to the standard in a number of cases, toxicology data suggested that the presence of anionic surfactants was undesirable. The cost of the surfactants was also prohibitive in some cases.

Further work was aimed at reducing the levels of anionic surfactant, and therefore by implication, the toxicity of the formulation. This would also reduce the cost. These studies eventually led to the adoption of a 50/50 blend of sodium dodecylbenzenesulphonate with nonylphenol (8) ethoxylate as a suitable wetting system; the total surfactant concentration was 7%.

Despite later attempts to find alternative wetting systems, this formulation is still the basis of many built-in-wetter Gramoxone formulations. A current programme of work is aimed at identifying suitable alternatives for the nonylphenol ethoxylate while providing an improved skin irritancy profile.

REFERENCES

REPORTS: PJ21/75/1C ; AR 2609C; AR 2896C;TMY258B

2.4 MULTIPLE EMULSIONS

Tadros et al, Jealott's Hill, 1987-1990

In the mid-1980's, multiple emulsions were chosen as a possible means of delivering safer paraquat formulations. This work was based on the premise that, because the paraquat solution was contained within a layer of oil, such formulations would be considerably less toxic than Gramoxone.

Early work was directed towards meeting the following criteria:

(i) >5-fold safening relative to GramoxoneTropics, translating to a >10-fold safening in 100 g/l formulations

(ii) no greater than a 5% loss in bioefficacy relative to Gramoxone

(iii) an incremental cost of formulation not exceeding £1000/tonne PQ ion, based on 1987 prices.

More than 300 formulations were initially tested in rats; the object being to investigate the effect of different compositions, as well as various process routes. The degree of safening obtained was a function of the properties of the oil layer, which depend on the nature of the oil, the thickness of the oil film, and the effectiveness and nature of the emulsifiers and any other additives. Increasing the thickness of the oil film meant that the paraquat content of the formulation had to be necessarily reduced.

About 30 formulations which showed at least a 2-fold safening effect were further tested in dogs, The best of these, a formulation designated E26, was based on a system containing, diesel oil, Atlox 4912, Synperonic NPE 1800, and 2M NaCl, and had a X6 safening effect. However, this formulation also had the draw-back of having very poor dispersion characteristics, and producing a gel on storage.

Further work was therefore aimed at improving sprayability of similar formulations. Several approaches were tried, including reduction of the volume fraction of the oil phase; however, this led to an unacceptable trade-off with the safening properties. Extensive screening tests on alternative oil systems were also unsuccessful.

The use of alternative stabilising salts such as $CaCl_2$ and $MgCl_2$ improved the dispersibility of the formulations to some degree, but they continued to be

very sensitive to the quality of diesel oil. Formulation strengths above 100 g/l were never achieved, meaning that a robust internationally marketable product was therefore not obtained. These problems led to the termination of the project in 1990.

This work did, however, provide information on the gastrointestinal uptake of paraquat (Section 3.7). Following a subsequent programme of work at CTL, $MgSO_4$ was identified as the most toxicologically beneficial soluble salt. formulation. This now forms the basis of a project to find a universally available antidote to paraquat poisoning.

Attempts were also made to encapsulate some of the more promising formulations in order to improve sprayability and increase safening effects (Section 2.5.2).

A number of emulsions containing various salts were subjected to skin irritancy tests in rabbits. In all cases the formulations were found to be less irritant than Gramoxone.

The following technical issues remain unresolved:

(i) Concerns over the sensitivity of the formulations to quality of diesel oil, and hence their robustness.

(ii) Suitability for spraying using a wide range of sprayers.

REFERENCES

REPORTS: TMY 387C

PATENT: APPLICATION GB 2247622

RAW DATA: Laboratory Notebooks D4572; D5020; D5409; D5846

2.5 MICROENCAPSULATED FORMULATIONS

2.5.1 US Formulations - *Scher et al, WRC, 1988-1989.*

A programme of work employing microencapsulation technology to safen paraquat formulations was undertaken at the WRC in 1988/1989 as part of an

"Under the Bench" exercise. The system tested was based on a microencapsulated paraquat solution dispersed in an oil. The walls of the microcapsule were formed of urea/formaldehyde, with diesel oil being used as the non-aqueous phase. Paraquat concentrations of up to 21% w/v were achieved; no attempt was made to incorporate wetters.

The opinion was that the formulation would be considerably less toxic, both from an oral and a dermal standpoint, because of the presence of the microcapsule wall and external oil phase. Conversely, it would be easily dilutable because of the high solubility of paraquat in water.

Preliminary testing at WRC showed the microencapsulated formulation to be X2 safer in rats than paraquat solutions of equivalent strength. Dermal toxicity was markedly improved, the formulation being classified as a mild eye irritant, and a moderate skin irritant; an aqueous solution of paraquat, by comparison, was a severe eye irritant and corrosive to skin.

However, oral safening effects were not borne out by further testing in dogs, presumably because the digestive juices in the stomach were too efficient at stripping off the non-aqueous phase, and dissolving the microcapsule wall at an earlier stage than expected.

The project was therefore shelved. The idea of incorporating magnesium salts into the formulation was recently discussed, but has been discounted as having no perceivable advantage.

REFERENCES: WRC Toxicology Report T-13489, and personal communications.

2.5.2 UK formulations - *Tadros, Brown et al, Jealott's Hill, 1988 - 1995*

The objective of this programme has been to improve the properties of paraquat multiple emulsions. Problems were encountered over sprayablity of the diluted multiple emulsion (Section 2.4), as a result of the rupture of the oil membrane on dilution.

Encapsulation using polyurea at the outer oil/water interface, giving in effect a "solid" dispersion, was thought to be one possible means of stabilising the membrane . This would give an EC formulation containing aqueous microcapsules of paraquat- essentially the reverse of conventional CS formulations wherein oil drops are microencapsulated in a water environment.

On dilution in the spray tank, the microcapsules would rupture, releasing paraquat into the spray solution.

This has now been achieved, with these microencapsulated formulations possibly adding to the safening effects seen for simple multiple emulsions.

However, these improved formulations are still only based on an initial paraquat ion content of 100 g/l, and unless this can be improved, such formulations are likely to be prohibitively expensive to produce/market.

Work in this area continues for a PhD thesis.

REFERENCES

Personal Communications (Report in Preparation).

2.6 "AUTOENCAPSULATING" FORMULATIONS

Knowles, Bull et al, Yalding 1987

A limited programme of work on "autoencapsulating" paraquat was carried out at Yalding in 1988. The idea was to incorporate components into the formulation that would 'gel' around the paraquat in the acid environment of the human stomach, thereby preventing uptake. (NB this principle was later employed in the 'Magnoxone' formulations.)

Formulations were based on a 20% w/w paraquat ion concentration, without any dye, stench or built in wetters. A variety of encapsulating systems were tested in the lab, using hydrochloric acid to cause gellation. These included:

(i) Polyethylene oxide with styrene/maleic anhydride copolymer

(ii) Polyvinylpyrollidone with polymethylvinylether/ maleic anhydride copolymer

(iii) Polyvinylpyrollidone with polymethylvinylether/ maleic anhydride and styrene/maleic anhydride copolymers

(iv) Polyvinylpyrollidone with polyacrylic acid (various molecular weights)

(v) Polyvinylpyrollidone/fumed silica with polyacrylic acid

(vi) Polyvinylpyrollidone with polyacrylic acid and styrene/maleic anhydride copolymer

(vii) EDTA/calcium chloride/sodium alginate (various grades)

Paraquat capsules were obtained at pH ca 2 in most cases but tended to leak in vitro. The process had additional drawbacks in that it necessitated the use of solid paraquat dichloride to achieve high paraquat concentrations, leading to increased hazards.

The project was therefore perceived as offering no safety advantages, and discontinued without any animals being sacrificed for toxicity testing.

REFERENCES

RAW DATA: Laboratory Notebook D4887

2.7 MAGNOXONE

Grabham, Donaldson, Shaunak, et al, Yalding 1989 - 1995

Attempts to stabilise multiple emulsions of paraquat with salts (Section 2.4) in the late 1980's led to the interesting discovery that magnesium salts had a marked effect on the uptake of paraquat in the gastro-intestinal tract. This sparked off a major programme of work at CTL, resulting in the development of the "Magnoxone" formulations.
The following product specification was defined by BSD:

- x5 safening with respect to Gramoxone
- <5% separation
- >90% bioefficacy with respect to Gramoxone
- acceptable sprayability using existing application methods
- <10% cost increment with respect to Gramoxone

Safening was effected by the incorporation of three main ingredients - magnesium trisilicate, magnesium sulphate, and additional emetic- into a standard 200 g/l Gramoxone formulation.

Magnesium trisilicate is thought to form a gel around paraquat in acidic (stomach) environments, preventing absorption of the paraquat and aiding in its removal by the combined action of magnesium sulphate and increased levels of emetic.

It should be noted, however, that all attempts to cause either magnesium trisilicate suspensions, or various Magnoxone formulations, to gel in acidic environments in vitro were unsuccessful.

Twenty three formulations containing various magnesium salts at different levels were ultimately tested for bioefficacy; these are summarised in an Exit Report on this project, to be published shortly.

The lead formulation, YF8004A, exhibited >x10 safening with respect to Gramoxone and appeared to meet all other criteria. It was subsequently scaled up and field tested in the early 1990's, but proved to be physically unstable at tropical temperatures. This resulted in the formation of a supernatant which contained no magnesium trisilicate, and as a consequence led to a reduction in expected safening.

Further work led to the incorporation of dispersant, to give a stable formulation (YF9677) with ca x10 safening. A reduction in pyridine base levels (YF9622) in line with Gramoxone Tropics gave a concurrent decrease in safening to ca X5. The mechanism of safening by the higher levels of pyridine bases is not really understood.

Despite meeting the initial target, the safening effect was regarded as insufficient to warrant full Development against a background of the successful stewardship campaigns mounted by the Company, which have significantly reduced accidental poisoning incidents.
The project was shelved in 1995 without any attempt at scale-up. This formulation is now unacceptable for development as it contains an alkylphenol ethoxylate, but the proven beneficial effects of magnesium sulphate are currently being exploited in a CTL project aimed at developing an effective antidote to paraquat poisoning.

The following issues remain unresolved for "Magnoxone" formulations:

(i) Would the safening work with humans?

(ii) Can the product be scaled up to give the desired physical properties (avoidance of foaming and formation of a supernatant layer)?

REFERENCES

REPORTS: TMY 387C

RAW DATA: Laboratory Notebooks D6376; D7485, D7974; D8539

PATENTS: Application GB2263067 (Unconfirmed grant).

3. SOLID FORMULATIONS

The two major targets for a universally acceptable solid formulation, apart from satisfactory bioefficacy are

(i) High active loading to avoid bulk.

(ii) Complete avoidance of dust during manufacture, transport, and storage, combined with ease of application using a wide range of sprayers.

Much work has been done within the Company on solid formulations over the last two decades, and this is summarised in the following Sections.

It is, however worth noting that dust standards have changed considerably over the past few years, and formulations that may have been regarded as "non-dusty" in the 1970's and 1980's may no longer meet modern standards of dustiness.

The technology required to design, build and operate a plant capable of producing paraquat formulations meeting current standards needs to be significantly different to any seen before within Agrochemicals formulation. There are major requirements for containment and control in terms of toxicity, coupled with production volumes which are much greater than seen before for solid agrochemical formulations. These types of containment/control requirements are generally applicable to the pharmaceutical industry but not at these large volumes. Therefore, there is a major concern over hygiene, containment and control of a plant of this type and **it is uncertain whether engineering/technical solutions are currently available to deal with these problems.**

For the formulations described below, therefore, the following technical issues remain of concern:

(i) The ability to scale upto a manufacturing scale whilst retaining the desired physical properties.

(ii) The ability to scale up a process without compromising internal SHE standards.

(iii) The control and minimisation of dust during the product's life.

(iv) The performance of such products in a wide variety of application equipment (eg knapsack sprayers).

REFERENCES

REPORTS: TMY0779C

3.1 EXTRUDED PROCESSES

Middleton, Drewe, Knowles, Donaldson et al, Yalding, early 1960's -

Work in this area started with the development of a "Weedol" granule at Yalding in the early/mid 1960's.

The process involved combining a paraquat/diquat/wetter mixture with a blend of dried magnesium sulphate, dye, and a second wetter. This pre-mix was then extruded, and the product dried and sieved to give granules of the desired size.

The product was aimed specifically at horticultural markets, and early formulations contained both paraquat and diquat. However concerns over the toxicity profile led to the omission of diquat (I) from the formulation eventually launched in 1964. This product contained 5% w/w paraquat ion, and was marketed under the tradename "Weedol".

Numerous changes have been made to the formulation and the process over the intervening years, and several new formulations developed.

Although formulations of up to 15% w/w paraquat have been successfully produced on a manufacturing scale, the process remains sensitive to the degree of drying and quality of magnesium sulphate. A low level of dust is obtained with the Casella test, but this is not sufficiently rigorous to predict the extent of problems that will be associated with dust in full commercial manufacture and use.

Regulatory restrictions on horticultural products, combined with market requirements have meant that only three formulations are produced by Zeneca on behalf of Miracle Garden Care Ltd:

- new "Weedol", containing 2.5% w/w paraquat and 2.5% w/w diquat;

- "Speedway, containing 8% w/w paraquat; and

- "Pathclear", containing 2.5% w/w paraquat, 2.5% w/w diquat, 5% w/w simazine, and 3% w/w aminotriazole.

These formulations are not sufficiently dust free to make them acceptable for larger packs for professional use.
Work on a newer version of "Pathclear" to replace the simazine in the formulation on behalf of Miracle Garden Care Ltd has recently been shelved.

REFERENCES

REPORTS: MD9354; PP/E/177; AR2324B; TMY5; TMY54; TMY 290C; TMY291B; TMY548B; TMY346C; RY0064B.

RAW DATA Laboratory Notebooks D4298 and D4887.

PATENTS: GB 1086937

3.2 FLUID BED GRANULATION

McCombs, Robson, Knowles et al, Yalding 1973 - 1985

The process consisted of spraying an aqueous paraquat/wetter feedstock onto an inorganic carrier fluidised by hot air in a fluid bed granulator. The water was evaporated off leaving a dry, free-flowing, "relatively dust-free" product.

Early formulations contained 20% w/w paraquat with 5% w/w Synperonic NP8 as wetter. Attempts were made to incorporate 10% w/w wetter, but resulted in unacceptably sticky grains. Later formulations contained a 1:1 blend of Synperonic NP8 and Synprolam 35X15. This formulation was designated YF7334 and was stable on storage, with acceptable dispersion properties. However, although patented, the formulations were never commercialised at the time because of cost implications.

Such a "relatively dust-free" formulation would no longer be regarded as acceptable.

REFERENCES

REPORTS: TMY 290C; Personal Communications

PATENTS: GB 1555489

3.3 HOT BELT/DRUM DRYING "FLAKE" PROCESSES

3.3.1 Chevron Carbowax Process

Knowles et al, Yalding, 1974 - 1976

This process was initially patented by ICI Australia, and developed further by Yalding in conjunction with Chevron, USA.

It involved concentration of paraquat solution under vacuum, followed by addition of carbowax (polyethylene glycol, MW 6000) to the hot concentrate. The mixture was homogenised and poured onto a rotating cold drum, where it solidified to give a product containing ca 50% paraquat ion. The solids were scraped off and sieved to give the required size.

The process was limited to production of high strength formulations (>32%), and was prone to foaming and solidification problems during the water evaporation stage. The problems with foaming were due to the presence of a wetting system. Removal of the wetter to meet EPA demands led to solidification problems, particularly at pilot plant scale. There was also some dust formation.

These technical problems, combined with the high capital costs involved led to the project being shelved in 1976. There was a brief revival of interest in the process in the 1980's but once again unresolved technical issues coupled with potentially prohibitive manufacturing costs led to the project being terminated without any commercialisation.

Note: Packaging of the flakes in water soluble bags was considered in the 1980's as a possible way of overcoming problems of dust exposure, but not investigated further.

REFERENCES

REPORTS: TMF 2300C, TMF 2346C, TMY 337C.

3.3.2 Kelco Matrix Process

Knowles et al, Yalding 1984 -1986.

This was similar to the carbowax process in that it involved mixing of paraquat concentrate with a "matrix", pouring onto a rotating drum, and scraping off the resultant solid. This was then sieved to give the correct size. The major difference was that in this case the paraquat concentrate was not pre-heated, but the drum was.

Studies were carried out in conjunction with Kelco, a subsidiary of Merck which produced the matrix. Kelco declined to reveal the exact nature of the matrix but it was thought to be a modified alginate, possibly in mixture with a second material eg gelatine. A subsequent "improved matrix" was thought to be modified xanthan gum.

Paraquat ion strengths of ca 35 - 60% w/w were achieved, without any attempts to incorporate a wetter system. However, "Matrix I" gave an insoluble precipitate on dilution, although this was subsequently resolved with "Matrix II". The process had further major drawbacks in the large amount of matrix required (x1.5 paraquat ion concentration), and its prohibitive cost. This, coupled with a contentious patent application by Merck meant that the process was not adopted.

This area of technology was subsequently exploited in the "Yalding Salt Process" (Section 3.3.3).

The option of packaging a paste in water soluble bags, thereby removing the flaking step, was also discussed, but not fully pursued.

REFERENCES

REPORTS: TMF 2300C; TMF 2346C; TMF 2355C; TMY 337C;

RAW DATA: Laboratory Notebook D4298.

3.3.3 Yalding Salt Process

Knowles et al, Yalding, 1986 - 1988.

The prohibitive cost of the Kelco "matrices" and a contentious patent application by Merck led to the search for suitable replacements for use in similar processes. In addition, the paraquat concentration in the flake had to be reduced to 20% as the higher strength product posed registration problems.

Work was initially concentrated on finding suitable materials for blends with the Kelco matrices. These included ammonium chloride, which gave quick dispersing, non-friable, low dust granules. Further work then attempted to reduce the amount of "matrix" in the blend, and eventually granules were successfully produced (without any matrix) by using ammonium chloride alone.

Blends of ammonium chloride with magnesium sulphate gave "virtually dust-free" granules, but these were not as free-flowing or readily dispersible. Magnesium sulphate used alone gave "slightly dusty" product; sodium chloride gave an unacceptable formulation.

Wetters were incorporated into some formulations, and a paraquat/ diquat mixture was also produced. Processing techniques were developed to give product containing upto 32% w/w paraquat ion.

This process, for the production of low-dust paraquat flakes in the absence of polymeric fillers, was patented but not commercialised at the time because of high capital costs.

A current evaluation of such a product would exclude it from consideration due to the presence of some fines and the risk of friability leading to yet more dust.

REFERENCES

REPORTS: TMY 290C

RAW DATA: Laboratory Notebooks D4298 and D4887

PATENTS: EP 0273551

3.4 SPRAY DRIED PROCESSES

Seaman et al, Jealott's Hill and Yalding , 1967 - 1968.

Some work was carried out, in this area in the late 1960's, but abandoned in favour of the extrusion process, which gave a less dusty product.

REFERENCES

REPORTS: TMJ 206B;TMJ 287B; TMJ 303B

4 OTHERS

4.1 JAPANESE FORMULATIONS

During the mid to late 1980's ICI assessed several solid paraquat formulations developed by SDS Biotech KK. All were based on ca. 18% paraquat ion content, and contained a gelling agent. These formulations were perceived to have an additional benefit in that a relatively dilute solution had to be prepared before the formulation was pourable.

The most promising formulations were relatively dust-free, but had unacceptable application properties due to the viscous nature of the spray solution.

Furthermore, although a two-fold reduction in acute toxicity relative to Gramoxone was exhibited in an initial rat study, this was not observed in subsequent dog studies.

The project was therefore shelved.

Reputedly safer paraquat "analogues" were also initially tested, but were not perceived as offering any significant advantage, and were therefore not pursued.

REFERENCES

REPORTS: TMY 336C; TMF 1781B; Farrell GM, "Technical Assessment of Paraquat WDG Formulation", September 1988;

RAW DATA Laboratory Notebooks D4298 and D4887

4.2 MISCELLANEOUS

References to other techniques such as agglomerates, briquettes, and effervescing granules may be found in the notebook referenced below, but little additional information is available.

REFERENCES

RAW DATA: Laboratory Notebook D4887.