

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

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:-

<u>Code</u>	<u>Primary</u>	<u>Secondary</u>	<u>Oil</u>	<u>Electrolyte</u>
82	B246	NPE 1800	DIESEL	CaCl <sub>2</sub>
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 <sub>2</sub>

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 Arlancel 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<sub>2</sub> molarities and different volume fractions have tried to optimise such a system. For instance, 0.75M MgCl<sub>2</sub> 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<sub>2</sub> being replaced with MgCl<sub>2</sub>.

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 (13 $\mu$ g/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 examine 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 commercial 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.

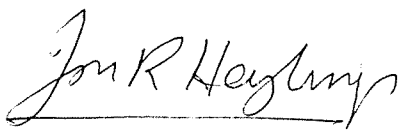
7. TRC MEETING

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

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|----|-----------------------|--------|
| 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).



DR JON R HEYLINGS  
BIOCHEMICAL TOXICOLOGY, CTL

CIRCULATION

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