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AN EMETIC FORMULATION OF 'GRAMOXONE'

Efforts to reduce the risk of accidental or suicidal ingestion of paraquat-containing formulations have been in progress for many years in response to, initially, a growing number of accidental deaths, which, in turn, led to pressure on ICI and its agents overseas by registration authorities. This pressure was felt particularly in Western Europe, where paraquat products have, since 1969, been increasingly severely classified.

The addition of an emetic agent was one line of approach that was explored and, until early this year, abandoned as being of little practical value. However, a compound has now been discovered that, when added to 'Gramoxone', shows every indication of fulfilling the functions that we require of it. These are:

- i) That it will product rapid and effective vomiting in man at low concentrations and with no adverse side effects. It is believed that this will greatly reduce the risk of death following the ingestion of paraquat.
- ii) That it is stable and will not affect the physical or chemical stability of paraquat formulations to which it is added.
- iii) That it will not adversely affect the herbicidal action of paraquat.
- iv) That it will not give rise to any adverse toxicological or environmental effects.

This compound, coded PP796, was developed by Pharmaceuticals Division between 1968 and 1972 as a potential drug for the relief of asthma. Toxicological studies in mammals were completed to the satisfaction of the UK Committee for the Safety of Medicines, which granted a Clinical Trials Certificate. On the basis of this Certificate, trials on humans were carried out in the UK. It became clear from these trials and from data generated in monkeys and dogs that PP796 was an effective and reliable emetic agent of considerable potency. For this reason the development of the compound as a therapeutic agent was abandoned.

The rapidity of action and acceptable toxicological characteristics of PP796 give it an advantage over other known emetics and it was chosen, in January, as a likely candidate for addition to 'Gramoxone'. Since then, a programme of work has confirmed the preliminary hopes. This work is continuing to satisfy all the criteria necessary for the acceptance of PP796 as an addition to 'Gramoxone' on a commercial scale and to meet the demands of registration authorities of any country in which it is decided to sell such a product. Results obtained to date and details of work in hand and projected are set out below.

1. Formulation

The level of inclusion of PP796 in 'Gramoxone' has, after careful consideration of human data, been established as 0.05% w.v, i e 5 mg in 10ml of 'Gramoxone'. This is confidentially expected to produce vomiting within 15 minutes in 75-85% of those ingesting such a quantity, which is the approximate minimum lethal dose of 'Gramoxone' in man.

It is now clear that both 'Gramoxone' and 'Gramoxone' S can be formulated with PP796 and storage tests after three months at -5° , 0° , 25° , 37° , and 50° C show no physical or chemical problems. The 'Gramoxone' formulation, coded JF 6043 is identical to the current product with 1% stench (pyridine base), 10% wetters and no corrosion inhibitors that will soon be in use throughout West Europe.

The PP796 which has been used in tests to date has been of pharmaceutical grade and the stability of a formulation made up with PP796 of 90% purity is being checked.

2. Process Chemistry

Pharmaceuticals Division are confident that they are able to produce tonne quantities of PP796 of the selected grade and that its incorporation into 'Gramoxone' can be achieved without major problems.

3. Patents

Formulations of paraquat containing PP796 have been the subject of patent filing in the UK and USA and will be protected in all major countries throughout the world. It is, therefore, essential that the composition of PP796 is kept highly confidential until filing has been completed.

4. Herbicidal Activity

PP796 has been shown, in glasshouse tests, to have no herbicidal properties.

Work carried out to date confirms our belief that the addition of PP796 at 0.05% has no adverse affect on the herbicidal activity of 'Gramoxone'.

Three series of small-plot trials have so far been completed.

The first, in the spring, demonstrated that the addition of PP796 at 500, 1000 and 2000 mg per litre of 'Gramoxone' had no effect on the degree or persistence of scorch of ryegrass over a five-week period after spraying.

A second series, on a predominantly ryegrass sward, showed no statistically significant differences between 'Gramoxone' and a tank mix containing the equivalent of 500 mg PP796 per litre of product. Scorch levels were high at all rates tested (300, 600 and 1200g paraquat/hectare) probably a result of the extremely dry conditions.

The third series, on potatoes, showed no significant differences in weed kill between the two formulations and in crop vigour one week after spraying.

Further trials with the formulated product are in progress on ryegrass swards and, on the farmer scale, on stubbles.

5. Emetic Efficiency

Experiments have demonstrated the effectiveness of PP796 in the presence of paraquat. Dogs were dosed with paraquat at a level that killed three out of four animals within four days. All animals in a second group, given the same dose of paraquat plus the emetic, vomited within 1 hour and paraquat blood levels were reduced. There were no deaths. Similar results were obtained with monkeys.

Further work is in hand to elaborate these findings, and acute oral, acute dermal, irritation and inhalation studies with the formulation JF64⁰⁴03 are in hand to meet possible demands by registration authorities. PP796 is rapidly absorbed, metabolised and excreted in rats, dogs, monkeys and man.

PP796 is not absorbed through skin and has low volatility. This, coupled with the extremely low level of PP796 in spray-strength material virtually eliminates any risk of operator hazard. Observations are now being made in the field on farm workers spraying the product as part of the large-scale development programme.

6. Environmental and Consumer Hazard

The fate of PP796 in the environment and in crops is being evaluated. Taint in plants and water, residues in plants, persistence and mobility in soil and water are currently under investigation.

7. Registration

The introduction of an emetic-containing formulation of 'Gramoxone' throughout West Europe will proceed as quickly as policy and registration procedures permit.

In the UK, limited clearance has been obtained for the use of 10,000 litres on approximately 2000 ha of stubbles and for other registered uses of 'Gramoxone'. It is currently intended to apply for full registration of a stented PP796-containing formulation for introduction at the beginning of 1977. The UK authorities are (apart from the safety aspect) treating this as a minor formulation change and, if trials continue favourably, no problem is envisaged. Registration of the current, stented formulation which expires on 31 December, 1976 will then be allowed to lapse.

The reaction of authorities in West Europe is less clear and a number of questions need to be answered if the Division's objective is to be achieved in the near future. For example:

- i) PP796 is herbicidally inert. It is, however, highly active pharmacologically. How is this likely to be viewed by authorities in the light of the current legislation on pesticides, bearing in mind the low level of addition?
- ii) If PP796 is seen as a drug rather than an inert ingredient, what legislation can authorities invoke and what would it entail in seeking registration?
- iii) How do agents consider the emetic concept can best be introduced to their national authorities - by personal discussion, by a formal approach alone, or by formal approach followed by discussion?
- iv) Given that some authorities are concerned at the number of paraquat fatalities, how quickly and how favourably are they likely to respond to any approach?
- v) Are there any important gaps in the work summarised above that must be filled before approaches can be made (e g here in France)?
- vi) If 'Gramoxone' is re-registered with an emetic, what bearing will this have on authorities attitudes to competitive paraquat products?