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PARAQUAT STRATEGY - FORMULATIONS

I attach a discussion paper on paraquat formulations. The paper is meant to provide a substitute for a PSAC (Paraquat Strategic Action Committee) meeting that proved impossible to set up.

The objective of the paper is to get widespread support and understanding for the direction that we are going with regard to safe formulations and specifically to seek your agreement to the recommendations of the paper.

These recommendations will provide the basis for the work that we wish to do over the next 12 months. This will obviously be discussed at the relevant TRC but I wish to be able to give direction to that work.

I would welcome any feedback and shall contact you within the next few days to solicit your comments or set up a meeting.

R A Morrison

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PARAQUAT STRATEGIC ACTION

SAFER FORMULATIONS DISCUSSION PAPER

SUMMARY

The acute oral toxicity of paraquat formulation has a significant detrimental effect on the sales of paraquat products and threatens their long term sales. In spite of ICI's efforts paraquat is still misused around the world with fatal results. Most of the fatal misuse is suicidal but this does not provide a secure defense for long term sales.

Much work on alternative safer formulations has been done and a number have been progressed to a state where they could, at a cost to both ICI and users, be introduced to markets.

The objective of a safer liquid formulation with little operational or financial disadvantage to users has, since 1986, been pursued using Multiple Emulsion technology. This has provided usable formulations but with some considerable operational penalties when compared to standard Gramoxone.

New developments using Magnesium Salts appear to offer better chances for success. These could possibly be introduced either with or without an increase in the current level of emetic. Any significant increase in emetic concentration would face a high financial penalty.

The current level of pyridine base stench is causing occupational health problems.

RECOMMENDATIONS

- 1 Work with the Multiple Emulsion formulations of paraquat is now formally stopped. The current lead formulation is effectively put "on the shelf" along with other "safe" formulations which have significant costs, financial and operational, to the user.
- 2 Technical development work is done to find an optimised Magnesium Salt formulation which maximises the safety of the formulation without operational inconvenience to the user. Given the very high cost of increasing emetic concentration this work should be done initially at the current level of emetic inclusion (0.5gm per litre).
- 3 The practical effect of a significant increase in the level of emetic in standard Gramoxone should be assessed on a test market basis. This to enable field assessment of the effect in human suicide situations of the results seen in laboratory animal tests.
- 4 The central recommendations for inclusion of pyridine base stench should be reduced in order to reduce occupational health problems. For tropical formulations the stench level should be reduced from 0.5% to 0.1% for temperate climates the current 1% recommendation should be renewed.

1 Background

The major threats to the continued profitability of our paraquat business are: i) The acute oral toxicity of the paraquat and the external perception that this gives the product ii) The soil degradation characteristics of the product (particularly when combined with media attention linked to i) above).

Experience over 30 years of sales indicates that, despite an oral LD50 to rat of 130mg/kg, the oral toxicity to humans is such that, for the 200gm ion/litre Gramoxone formulations most widely sold, the minimum lethal dose from ingestion is judged to be around 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 and 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 pressure over a long period from 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.

1.1 ICI's Reponse

From an early date ICI recognised its responsibility 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) acted as alerting agents to prevent accidental ingestion, and an emetic (PP796) to reduce the effective dose ingested. The result of these measures plus improved stewardship including education and training has been a very significant improvement in the numbers of accidental fatalities.

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. PP796 has not had any significant impact on survival rates at suicide dose levels.

ICI has always drawn a firm distinction between its responsibility 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. Our fundamental responsibility is to 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. (It is for this reason that a reduction in stench levels is now proposed, see 3.4). Regulators/media have not however always seen the distinction in the same terms as ICI. As a result the lobby against paraquat withdrawal remains. Demands continue to be made either for product withdrawal or for a change to 'safer' formulations in response to high levels of suicides. 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 it must be recognised that regulatory restrictions/withdrawals have led to a reduction in the Group profit and threaten future product sales because of a "band wagon" effect. This may be exacerbated by harmonisation of registration requirements or Prior Informed Consent guidelines.

Although we can defend ethically the position that we are not responsible for suicide. We must continue to be prepared to defend the product against regulatory attack with a strategy that recognises the real threats.

ICI has done considerable work in the areas of novel paraquat salts and the development of antidotes, neither of which have shown promise. The area of safer formulations has shown the greatest promise and is the subject of this paper.

1.2 Current Liquid Formulations

The current formulations of 'Gramoxone' containing 200gm ion per litre paraquat and using a 5-10% 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.
- They 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 £750/te ion. The current safening additives (blue, odour and emetic) add £150/te ion. In total therefore the formulation and packing adds £1150/te ion to the ai VPC of £2850/te ion.

2 Current Formulation Strategy

ICI's actions in including the safening additives in the current liquid formulations are in line with our responsibility to minimise accidental fatalities with paraquat. We see no reason to change proactively from our current formulations. However there has been and will continue to be a 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 has in the past approved the strategy of developing alternative formulations to a commercialisable state of 'on the shelf' readiness in order to provide a 'basket of options' to offer 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. At this dilution level, formulation and packing costs would be increased and product usage by farmers would reduce very significantly because of bulk inconvenience and 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 and variable cost terms. There are also significant concerns about dust from solid formulations both at the manufacturing stage and in the field. Whilst there are not insurmountable they increase costs and probably further reduce convenience.
- 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 helps to reduce oral toxicity and thus increase the minimum lethal dose for a given content of bipyridyl ion. The increase is modest. Diquat is more expensive to manufacture than paraquat (£700/te ion VPC) and is less effective on grass weeds. Under tropical and high sunlight conditions the addition of diquat adds little to the paraquat in mixed formulations and in some situations actually reduces regrowth control. The introduction of paraquat-diquat mixtures in certain circumstances 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 rates may have been only marginally reduced by this significant 4.5x fold reduction in paraquat content.

For the above reasons the strategy foresees, that alternative formulations would only be offered to regulatory authorities as an alternative to product withdrawal.

3 Safer Liquid Formulations

The Safer Liquid Formulation project has as its objective the development of a formulation that could maintain existing registrations for paraquat by producing a significant increase in the survival rate from poisonings (from whatever cause). This must be done without incurring an excessive cost penalty to the business and without reducing product effectiveness, convenience or safety to the farmer. Such a solution to the business problem described above would then be available as part of the current reactive strategy for paraquat regulatory crisis or possibly for consideration as the basis of a pro-active strategy for formulation change.

The Safer Liquid Formulation project has over the last few years concentrated on the development of Multiple Emulsions for a possible formulation. It was felt that this technology had had the potential for development to a degree that might enable a pro-active introduction of a safer formulations to be made. Work on this formulation particularly at CTL has improved our understanding of possible solutions to the toxicity problem. This has lead to some interesting developments.

3.1 Emetic Levels

After oral dosing in dogs paraquat reaches peak plasma concentration within 30-60 minutes. It is known that the toxicity can be reduced if the peak plasma concentration and the total paraquat absorbed can be reduced. Speed of emesis is therefore important. Increasing the emetic rate causes faster emesis in dogs. Present data from human poisonings suggests that the average time to emesis is 30-40 minutes. It is believed that a 5 fold increase in emetic would reduce the time to vomiting in man with the potential saving of a number of lives.

Vomiting does not completely empty the stomach and therefore serious suicide attempts would be unlikely to be affected by an increase in the inclusion of emetic.

3.2 Multiple Emulsions

Considerable work has been done on these formulations and a ME formulation has been developed which has a 10 fold safety factor compared with normal Gramoxone. This safety factor arises partly by dilution (10% product) giving a x2 safety factor, partly from the intrinsic characteristics of the emulsion (x2-3 safety factor) and partly from increased emetic concentration (x2-3 safety factor).

The dilution of the formulation and its sprayability is satisfactory but clearly not as convenient to use or to handle as Gramoxone. Manufacturing and packaging costs are high and the shelf life and scaling up of manufacture have not been evaluated.

3.3 Magnesium Salts

These are formulations with magnesium sulphate/magnesium trisilicate the latter forming a thick gel under the acidic conditions of the stomach. This causes the paraquat to become trapped in the gel with a consequent delay in its absorption allowing greater leeway for emesis or other treatment to be effective. It appears that the gel also delays absorption of the emetic. Current evidence suggests that these formulations may be 3-4 times less toxic than Gramoxone. This safety factor can be improved with higher rates of inclusion of PP796. This formulation is a thick pourable syrup which has a low added cost.

The intrinsic safety of this formulation appears at least as good as the ME without some of the disadvantages.

4.0 Stench Content of Gramoxone

The pyridine base is included in Gramoxone as an alerting agent to prevent accidental swallowing. The current level of inclusion are currently 1% in temperate climates and 0.5% for use in the tropics.

There have been many complaints, particularly from tropical area of occupational health and other problems arising directly from the pyridine base.

The disadvantage of the stench are:-

- 1) Chemical - nausea, headaches, loss of appetite.
- 2) General aroma - nuisance value causing some customers to revert to Taiwanese paraquat.
- 3) Complaints from pilots including refusal to use Gramoxone.
- 4) Association of the smell with inhaling paraquat which is known to be harmful to the lungs.

A number of countries have reduced the stench level without obvious disadvantage.