Paraquat formulations research proposal

Business objective & scope

'Safer' paraquat formulations

Short- mid-term delivery of commercially-viable formulation solutions

Human Safety needs to be in a position to provide the best possible advice to other functions, including but not limited to marketing, stewardship and formulation research, in the factors which are or may be important to include or exclude in the design if future paraquat formulations on a global basis. These formulations may include conventional 'straight' liquid (SL) formulations of paraquat alone or in combinations with other active ingredients (e.g. diquat, diuron).

What does the existing data tell us about what is or may be important?

Concentration of the active ingredient

Historically Syngenta has commercialised a wide range of formulations of varying paraquat ion concentration. Frequently at a concentration of 200 g paraquat ion/L but with a range of 360 g to 45 g/L. Solid formulations have been commercialised with a range of 25 to 80 g paraquat ion/kg. Clearly the higher the concentration of paraquat in a formulation the greater the amount of paraquat ingested for a given volume of formulation. Are there circumstances in which a 'dilution' approach is contra-indicated

The following questions may warrant further investigation:

I s there a linear relationship between the amount consumed and that absorbed ? Is less paraquat absorbed when the concentration of paraquat in the G I tract exceeds a certain concentration ?

Is there any evidence for an effect of the presentation of the formulation (i.e. liquid vs. solid ?) on the toxicity to laboratory animals ?

Is there any evidence for an effect of the presence of other active ingredients (e.g. diquat dibromide) on the toxicity to laboratory animals ?

Presence and concentration of the emetic PP796

The centrally-mediated emetic PP976 has been added to all paraquat-containing formulations since 1977 to cause rapid emesis following oral ingestion of paraquat to reduce the amount of paraquat in the GI tract available for absorption. PP796 is known to be an effective emetic. The typical concentration of PP796 in paraquat-containing formulations is 0.5 g/L however formulations with higher emetic concentrations also exist. At a standard concentration of emetic the dose to which an individual may be exposed will clearly increase according to the volume of formulation consumed

Presence, type and concentration of surfactants (e.g. Nonyl phenyl ethoxylate, sodium salt of dodecyl benzene sulphonic acid, C13-C15 alkylamine ethoxylate)

The great majority of global paraquat formulations (essentially those commercialised outside of the USA) include a built-in-wetter for improved biological (herbicidal) performance. In the USA the Distributor typically recommends an 'own brand' surfactant for tank mixing. A range of different surfactant systems have been used in both 'straight' and 'pre-mix' formulations and at a range of formulation concentrations and ratios of surfactant to paraquat (ion) content.

How significant is the presence / absence of a surfactant to the rate and extent of GI absorption of paraquat?

Is there a significant difference between alternative surfactant systems ?

Is there overlap in the extent of paraquat uptake within the GI tract between formulations containing (any) surfactant and those with no surfactant?

Is it possible to predict the impact of a given surfactant based on its structure and/or physico-chemical properties?

Is it possible to predict the impact of a given surfactant based on its *in vitro* or *in vivo* eye (or skin) irritation / corrosivity structure and/or physico-chemical properties?

Is the impact of surfactant the same in all regions of the GI tract (buccal cavity, oesophagus, stomach, instestine)?

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.

Presence, type and concentration of stenching agent

A stenching agent has been added to all liquid paraquat-containing formulations since 1977 to act as an alert that the material in the bottle is not a drink, e.g. cola. A range of different dyes have been used in both 'straight' and 'premix' formulations and at a range of formulation concentrations and ratios of stenching agent to paraquat (ion) content. Stenching agents include or have included pyridine bases and valearic acid. The effectiveness of the stench depends on its volatility from the formulation and therefore to some extent on the ambient temperature. There is a balance to be struck between the need to alert to the potential hazard and the nuisance a strong smell may have for the legitimate user (mixer/loader or spray applicator). It is for this reason that lower concentrations of stench are typically used in liquid formulations sold in warmer (tropical) countries.

[[Out of Scope \rightarrow Reducing the likelihood of (accidental) ingestion rather than a formulation solution to mitigate the consequences of ingestion]]

Does the stenching agent have any impact on the likelihood or effectiveness of emesis (incl. on rate or extent of absorption of PP796)?

Does the stenching agent have any impact on the rate or extent of absorption of paraquat?

Presence, type and concentration of colouring agent

A dye has been added to all liquid paraquat-containing formulations since 1977 to act as an alert that the material in the bottle is not a drink, e.g. cola. A range of different dyes have been used in both 'straight' and 'pre-mix' formulations and at a range of formulation concentrations and ratios of dye to paraquat (ion) content. Dyes include or have included sulfacide brilliant blue 5 J.

[[Out of Scope \rightarrow Reducing the likelihood of (accidental) ingestion rather than a formulation solution to mitigate the consequences of ingestion]]

Does the dye have any impact on the likelihood or effectiveness of emesis (incl. on rate or extent of absorption of PP796)?

Does the dye have any impact on the rate or extent of absorption of paraquat?

Presence and concentration of magnesium sulphate (MgSO4)

Magnesium sulphate has been added to certain (liquid) paraquat-containing formulations (e.g. Inteon, Magnoxone) to act as a purgative

Presence and concentration of magnesium trisilicate

Magnesium trisilicate has been added to certain (liquid) paraquat-containing formulations (e.g. Inteon, Magnoxone). 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.

Alternative salts (bipyridyl counter ions)

Effectiveness of emesis

Probability of occurrence, time to first occurrence, frequency, overall effectiveness at removing paraquat prior to systemic absorption

What is the effective dose ? (establish appropriate probability of occurrence)

How rapidly does first emesis occur?

[Other than for paraquat poisoning, emesis is not generally advocated in the treatment of poisoning as]

Absorption from:

Buccal cavity

Stomach

Jejenum

Closing

Animal data

Human data

Proposed further interrogation of existing studies

Proposed further studies

Human data

Proposed further interrogation of existing studies

Proposed further studies

Sri Lanka

Korea

Other (AHI)

Timetable

Resources required

Financial

Technical

Next steps

Sanctioning

References

General

J Tucker and C Formstone 'Alternative Bipyridyl Salts and Complexes with Reduced Mammalian Toxicity' Yalding Technology Report No. TMY1015B, October 2001

R Shaunak 'Safer Paraquat – A Summary' Yalding Technology Report No. TMY0801C, 1996

Surfactant systems

K A Walters, E A Lock, G D Mason and P H Dugard 'The effects of surfactants on the toxicity and gastrointestinal absorption of paraquat. Part I: The LD_{50} and gastrointestinal absorption of paraquat when administered to dogs as the formulation Gramoxone S and Gramoxone W' CTL/R/373, January 1976

K A Walters, E A Lock, G D Mason and P H Dugard 'The effects of surfactants on the toxicity and gastrointestinal absorption of paraquat. Part I: The LD_{50} and gastrointestinal absorption of paraquat when administered to dogs as the formulation Gramoxone S and Gramoxone W' CTL/R/373, January 1976

K A Walters and P H Dugard 'The effects of surfactants on the toxicity and gastrointestinal absorption of paraquat. Part III: The *In Vitro* absorption by dog: gastrointestinal mucosa of paraquat in the presence and absence of surfactant' CTL/R/375, January 1976

E A Lock, P H Dugard and K A Walters 'The effects of surfactant on the toxicity and intestinal absorption of paraquat. Part IV- comparison of various species including man' CTL/R/376, January 1976

K A Walters, P H Dugard and A T Florence 'Non-ionic surfactants and gastric mucosal transport of paraquat' J. Pharm. Pharmacol. Vol 33, pp 207-213, 1981

Absorption

I have conducted considerable research on the site and mechanism of absorption of paraquat through different regions of the GI tract. This is probably best summarised in:

HEYLINGS J R (1991). Gastrointestinal absorption of paraquat in the isolated mucosa of the rat. Toxicol Appl Pharmacol 107 482-493.

In this paper I compared the flux of a typical human exposure dose through isolated oesophagus, 2 regions of stomach, duodenum, jejunum, ileum and colon of rats. The absorption was only really significant in the small bowel and mostly in jejunum. This is because PQ is polar and having no lipohilicity (or fat solubility) can only gain access between the mucosal cells. Above and below the small bowel the epithelium has "tight" junctions between adjacent calls and molecules cannot diffuse easily between them into the blood. There is also a facilitated or active uptake of PQ in the small intestine (almost certainly a polyamine transporter) which carries the chemical through the cell, in addition to between cells. This makes regions like the jejunum a "window" for PQ uptake that we must avoid prolonged contact with to prevent high blood levels.

We also studied this in vivo in rats. The same differential absorption occurs when you surgically ligate and isolate different regions. I would anticipate that the absorption of PQ through human mouth, oesophagus and stomach is also very low, unless there is severe damage to the epithelium (as we showed in my publication above). This could potentially occur if the patient has a pre-existing stomach ulcer.

Document Metadata	
Author:	m221195
Last Modified Date/Time:	12/16/2008 12:00 AM
Last Modified Date:	12/16/2008 12:42 PM
Last Modified Time:	12:42:00 PM
Date Created:	11/7/2008 1:52 PM
Date Created/Time:	7/11/2008 12:00 AM
Time Created:	01:52:00 PM
Date Last Printed/Time:	
Last Accessed Date/Time:	
Earliest Date:	7/11/2008 12:00 AM

2008.12.16 Paraquat formulations research proposal SYNG-PQ-02023084 Metadata