A Novel Formulation of Paraquat to Improve Product Safety

March 18, 2004
Regulatory Background

- First registered in 1964
- Broad range of crops (burndown/dessicant)
- Ag use only, no home owner
- Restricted use
- Danger / Poison
- Emetic required in paraquat formulations (1987 Registration Standard)
- Dye and alerting agent added by Syngenta
Human Safety

Acute Toxicity

Accidental ingestion

Intentional ingestion
Dermal Toxicity

Skin Irritation

Nose bleed
Safety Improvement

Alginates (Sea weed extract)
- nontoxic gelling agents
- commonly used in the food industry
- Used in pharmaceutical industry for therapeutic properties (wound healing, treating dyspepsia)
• pH trigger causing gelling in the stomach improving effective emesis

• Potential for improving dermal irritation

• Excellent weed efficacy
Goals

- Improve oral toxicity in humans
- Improve dermal irritation
- Improve odor while keeping alerting properties

Paraquat AWT

Alginate
Dye
New Alerting Agent
Purgative
More Emetic

Gramoxone AWT Confidential Business Information syngenta
PARAQUAT ABSORPTION IN THE DIGESTIVE TRACT

Acute Oral Testing

- Must use vomiting species
- Dog study designed and completed (3 dogs)
- Literature / previous studies indicate 55 mg/kg is a lethal dose in dogs
- Baseline data from previous studies used for non-AWT formulation (at 44 mg/kg, just below lethal dose)
- Doses were 46, 92, 184, 368, and 736 mg/kg of formulated product

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Plasma paraquat following an oral dose (46 - 736mg formulation/kg b wt.) in dogs (n = 3)
Plasma paraquat AUC values following an oral dose of A3879BU (46 - 736mg formulation/kg b wt.) in dogs (n = 3)
Plasma emetic values following an oral dose of A3879BU (46-736mg formulation/kg bwt.) in dogs (n = 3)

Average time to 1st emesis (minutes)
- 46 mg A3879BU/kg: 51.3 ± 9.3
- 92 mg A3879BU/kg: 35.3 ± 3.8
- 184 mg A3879BU/kg: 26.0 ± 2.5
- 368 mg A3879BU/kg: 31.3 ± 6.7
- 736 mg A3879BU/kg: 20.3 ± 3.0
Acute Oral Toxicity Summary

- Significant reduction in absorption of paraquat in dog following oral ingestion
- Dogs tolerated 10 fold increase over known lethal dose
- Conservative estimate of a 5-fold safening for humans
- Essentially eliminating fatalities from accidental ingestion
Comparative skin irritancy – AWT 200 g/l and Gramoxone 200g/l formulations

Skin irritation: Erythema

Erythema Scores:
0  No erythema
1  Very slight
   (barely perceptible)
2  Well defined
3  Mod to severe
4  Severe (beet redness)

Days recovery

Mean score

AWT

A3879BU  Gramoxone 200g/l

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Comparative skin irritancy – AWT 200 g/l and Gramoxone 200g/l formulations

Skin irritation: Oedema

Erythema Scores:
0  No erythema
1  Very slight  
   (barely perceptible)
2  Well defined
3  Mod to severe
4  Severe (beet redness)

EPA Skin Irritation Category IV
Confidential Business Information
Comparative eye irritancy – AWT 200 g/l and Gramoxone 200g/l formulations

Irritation scores (Draize)

Days after instillation

Gramoxone

AWT

- Iris
- Cornea
- Conjunctiva
Comparative eye irritancy – AWT 200 g/l and Gramoxone 200g/l formulations

Eye Irritation EPA Category II
Confidential Business Information
Eye/Skin Irritation Summary

- Less irritating to skin
- Less irritating to eye

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Paraquat AWT

- AWT studies presented today on a 200g/l formulation with pyridine base alerting agent (CDN / Mex formulation)
- Additional studies are scheduled to evaluate a 240g/l formulation with new alerting agent (US formulation)
  - Need coordination with Inerts group for leaf alcohol approval for food use
- Production investment required as strict ‘pharmaceutical-like’ production conditions necessary
Next Steps

- Request Amendment of technical label / conditions of registration
- Submission of 200 g/l dog studies, overview of historical data
- Request ‘Joint Review’ process for NAFTA
  Will also discuss with CDPR
- Submission of 240 g/l acute toxicology, product chemistry studies, dog studies
Overview of Paraquat Use in Mexico

Maurilio Flores, R&D / Regulatory Director, Syngenta Mexico
Paraquat Use in Mexico

10%  70%  20%

Gramoxone AWT

syngenta
Overview of Mexican Use Pattern

- Between rows & preplanting

- Small farmers (> 2.0 Million users)
  - Average plot size 0.5 to 1.0 ha
  - Application with backpack sprayer
  - Main size container 1 liter

- Fields have a steep slope (subject to erosion)
- 3 - 4 applications per year

- Use of personal protection equipment rare due to climatic & cultural conditions
Registrants of Paraquat - Mexico

- 22 Registrants of Paraquat in Mexico
- 7 are supplied AI by Syngenta
- 15 are supplied by different sources, quality uncertain, do not follow FAO, US EPA specification requirements
How big is the issue in Mexico?

- Occupational exposure not a concern

- Regional authorities in major use area have perception of paraquat as a strong poison
  - Potential lethal risk due to easy access
  - Concern with incorrect use of pesticides (Syngenta / industry developed programmes to improve this situation)
  - Intentional ingestion a major concern

- Major area of concern is Chiapas State
Why Chiapas?

- Inappropriate product storage
- Areas of extreme poverty
- Low level of education
- Low level of agricultural technology
- Culturally divergent from other areas of Mexico
Registration of pesticide intoxication cases. MEXICO
official source (SSA, SAGARPA)

Year | # Of Cases
--- | ---
1998 | 6422
1999 | 5642
2000 | 2887
2001 | 2831
2002 | 2551
Intoxications in the State of Chiapas

No. of cases

AÑO

1998 1999 2000 2001 2002

84 112 85 55 31

41 45 29 21 18

48% 40% 34% 38% 58%

total       paraquat

Fuente: SSA Chiapas
Type of Intoxication
All Pesticides, State of Chiapas

Year
1998 1999 2000 2001 2002

No. de casos
0 10 20 30 40 50 60 70 80

Intentional
Accidental
Occupational Exposure

Fuen
LUPPA PROGRAM
Syngenta México .... Since 1987

LOS USOS PARA LOS PEQUEÑOS AGRICULTORES
Small Maize Grower –
Low Level of Technology

started: 1987
PRESENTATIONS

- Reading the product label
- Safety & hygiene preventive measures
- Application techniques
- Application timing
- Accurate disposal of empty containers
- Product storage
- Wearing protective clothes

FIELD DEMO PLOTS
# RESULTS: 1987 - 2003

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<th>Year</th>
<th>Presentat.</th>
<th>field demo plots</th>
<th>No. Farmers</th>
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<td>491</td>
<td>188</td>
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<tr>
<td>total</td>
<td>13,421</td>
<td>10,182</td>
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### TABLE 3 – PLASMA PARAQUAT AREA UNDER CURVE

<table>
<thead>
<tr>
<th>Dose received</th>
<th>Method of administration</th>
<th>Paraquat AUC (µg/mL.h)</th>
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<tr>
<td></td>
<td>mg formulation/kg</td>
<td>Mg paraquat ion/kg</td>
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<tr>
<td>Gramoxone</td>
<td>44</td>
<td>8</td>
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<td>(n=12)</td>
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<tr>
<td></td>
<td>Gavage</td>
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