

# **A Novel Formulation of Paraquat to Improve Product Safety**

**March 18, 2004**



**Confidential Business Information**



# 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**

# **Human Safety**

**Dermal Toxicity**

**Skin Irritation**

**Nose bleed**



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# 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)

# Paraquat AWT – Key Targets for Development

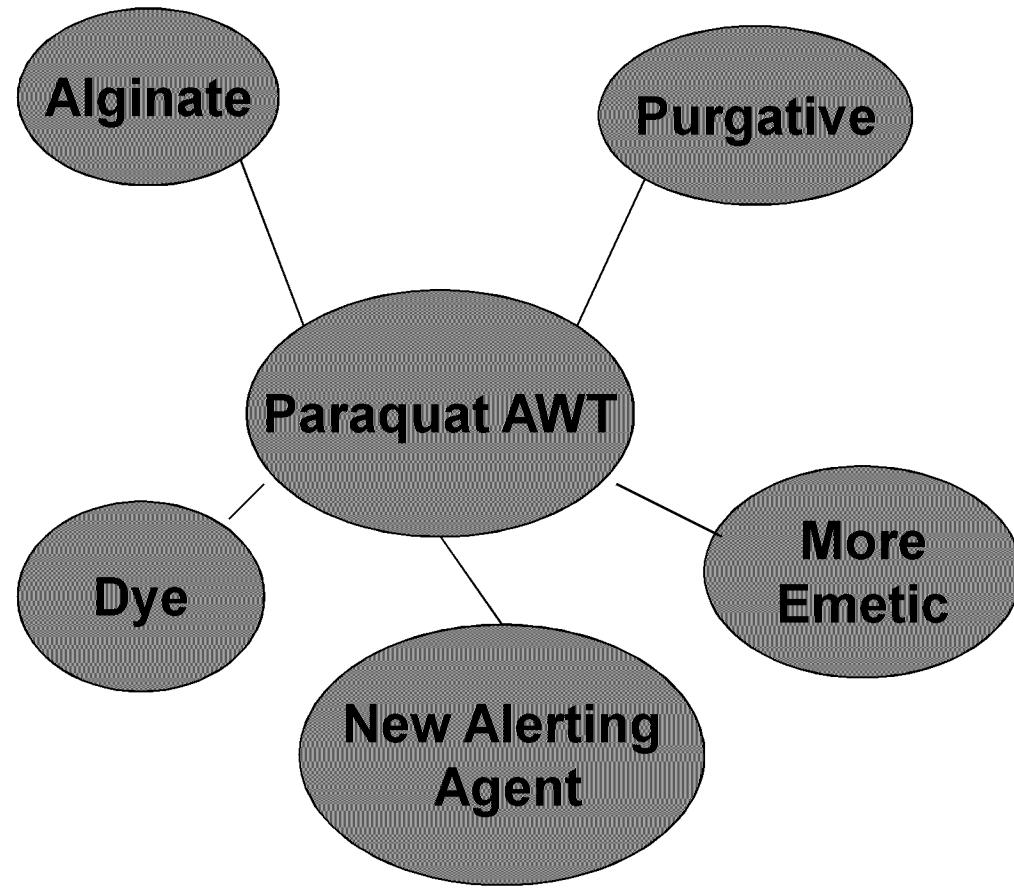
- pH trigger causing gelling in the stomach improving effective emesis
- Potential for improving dermal irritation
- Excellent weed efficacy



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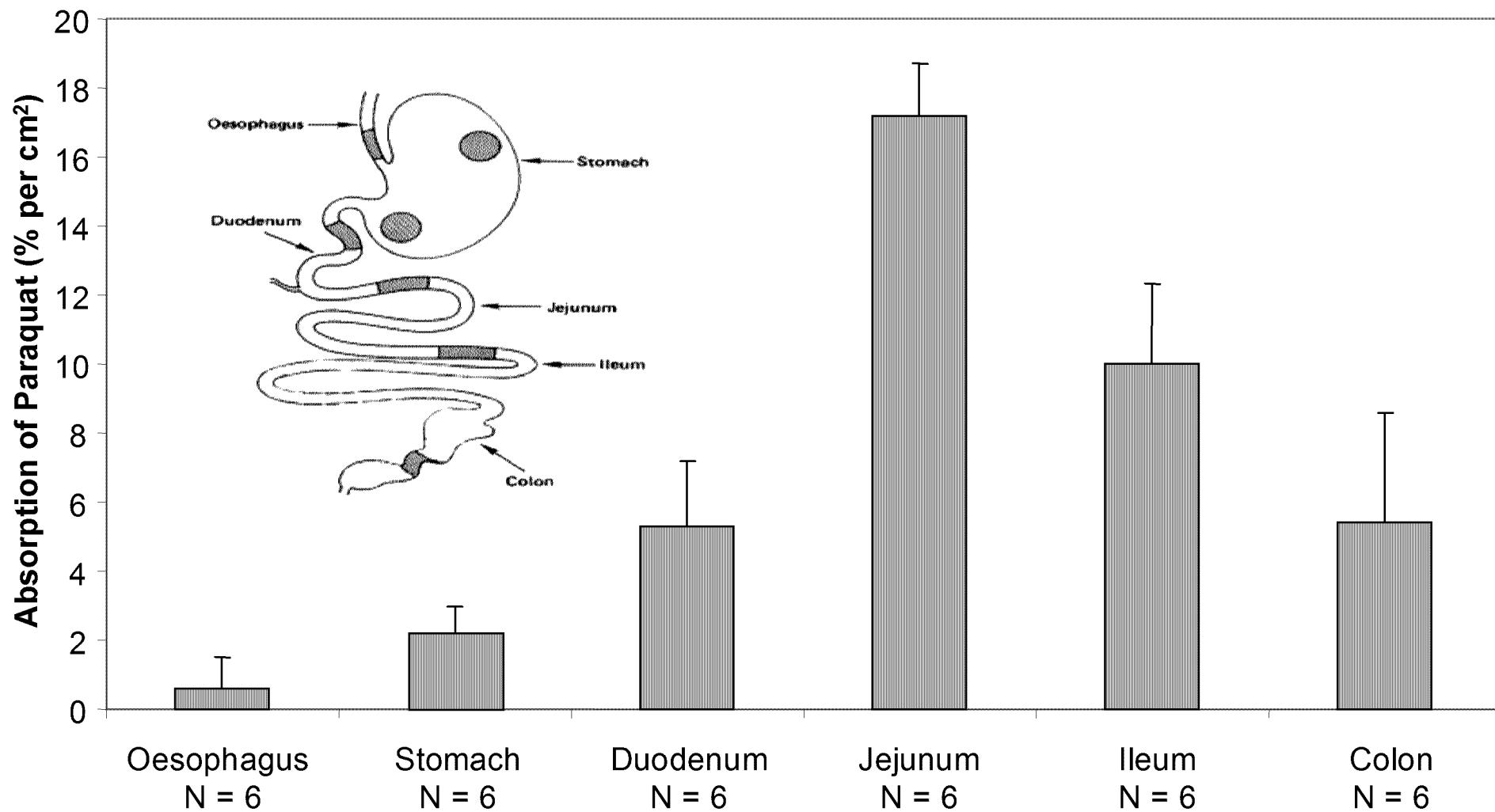
# Paraquat AWT Formula



## Goals

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

# PARAQUAT ABSORPTION IN THE DIGESTIVE TRACT



Gramoxone 

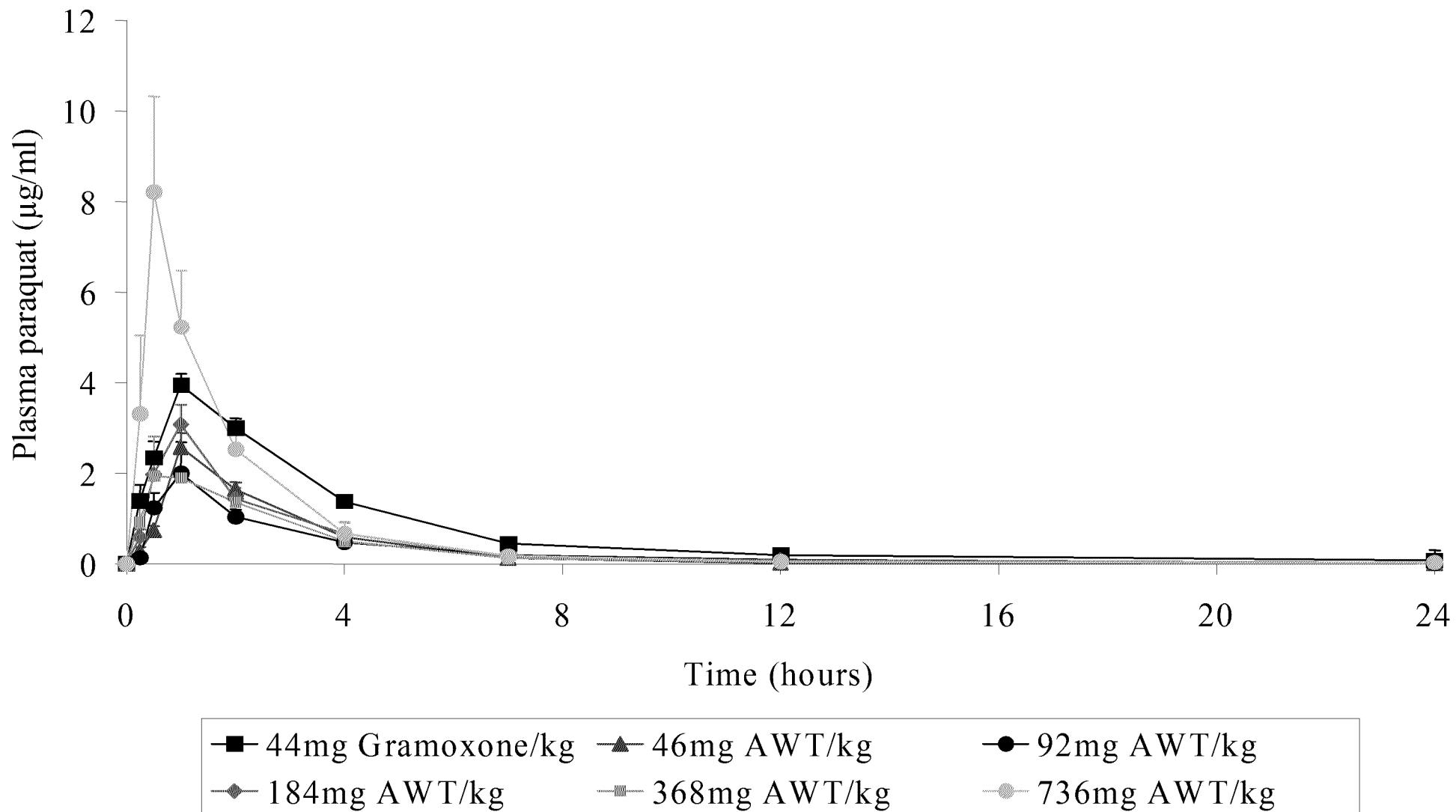
Heylings JR *Toxicol. Appl. Pharmacol.* 107, 482-493, 1991



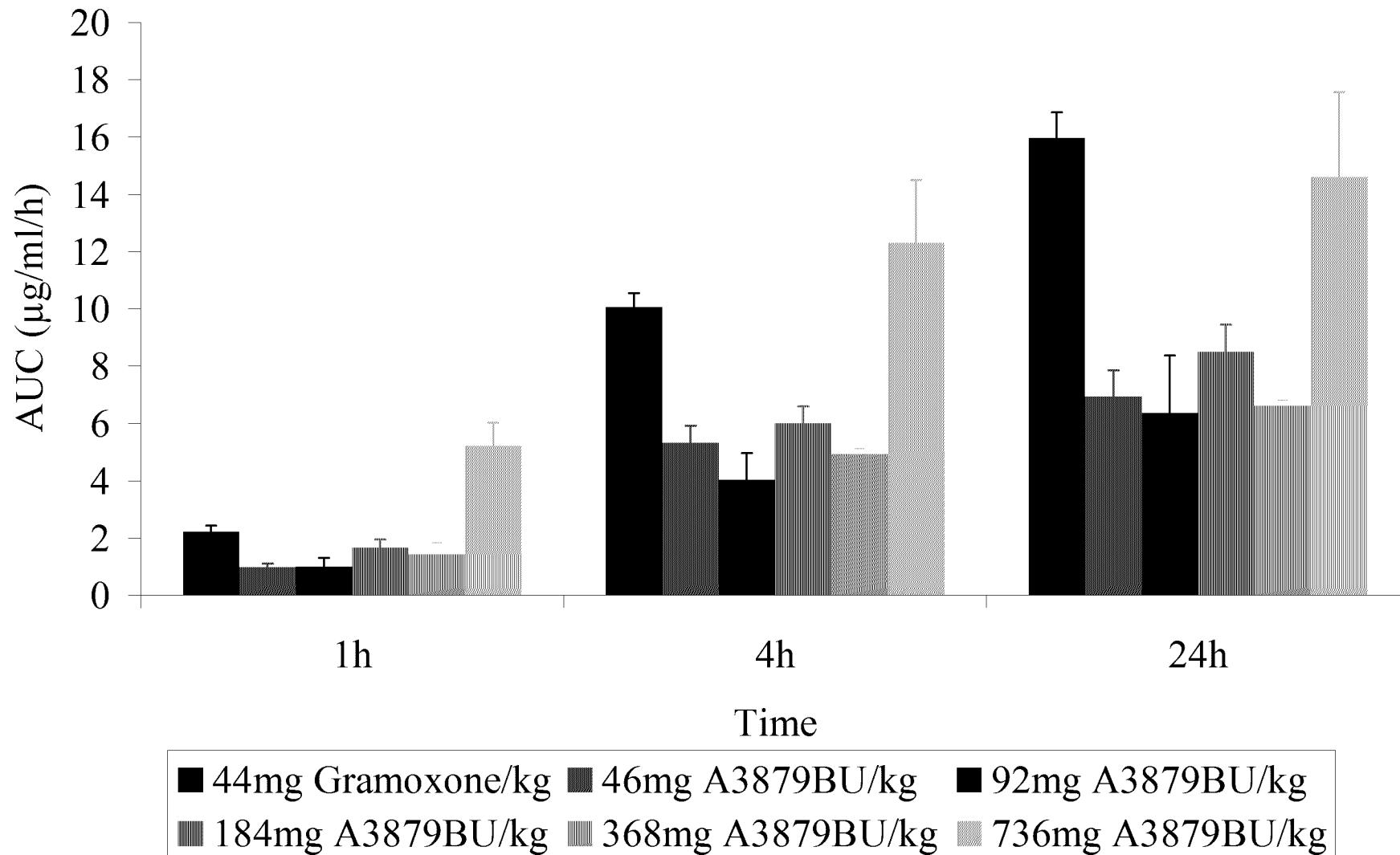
# Acute Oral Testing

- 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

# Plasma paraquat following an oral dose (46 - 736mg formulation/kg b wt.) in dogs (n = 3)



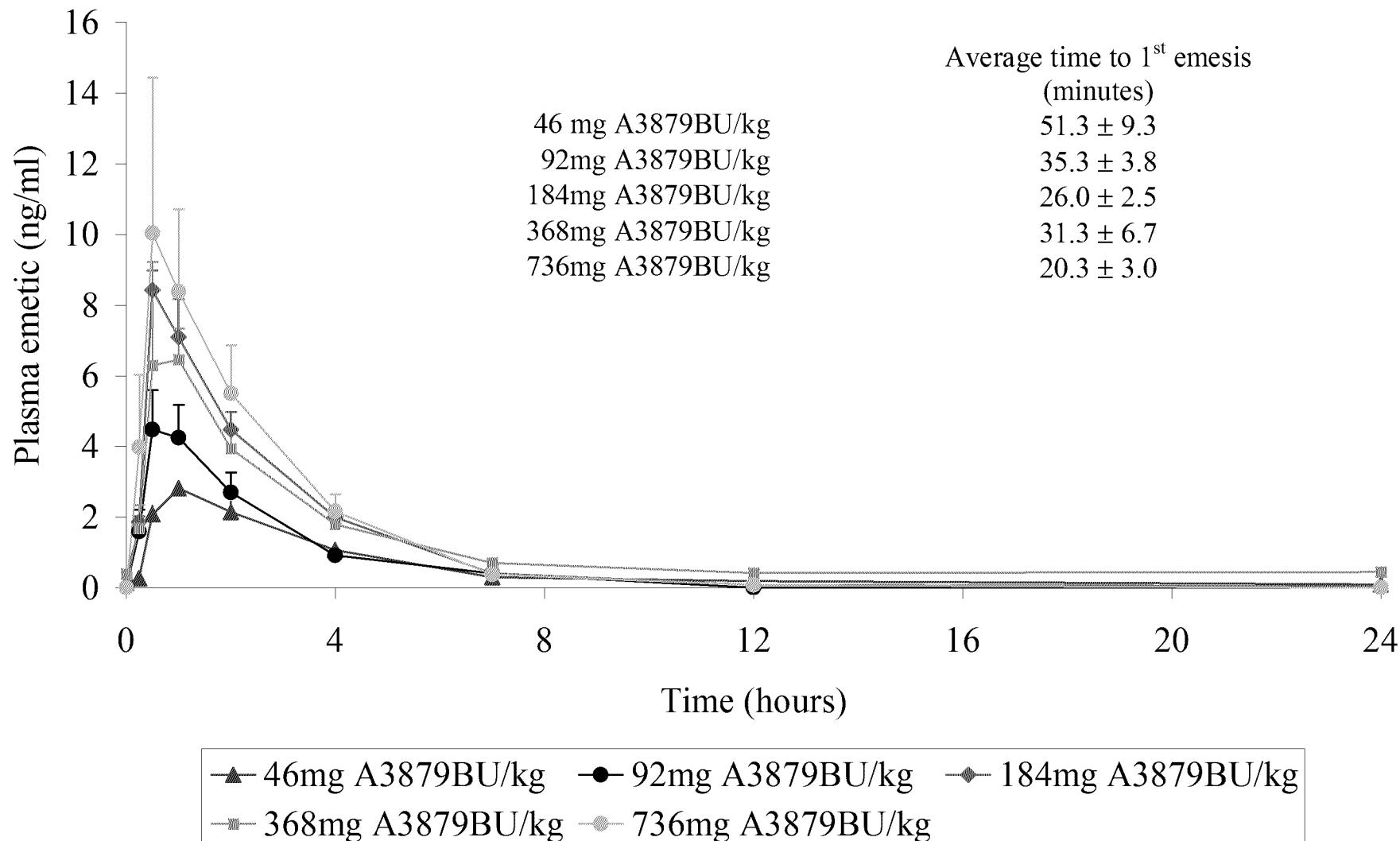
# Plasma paraquat AUC values following an oral dose of A3879BU (46 - 736mg formulation/kg b wt.) in dogs (n = 3)



Gramoxone

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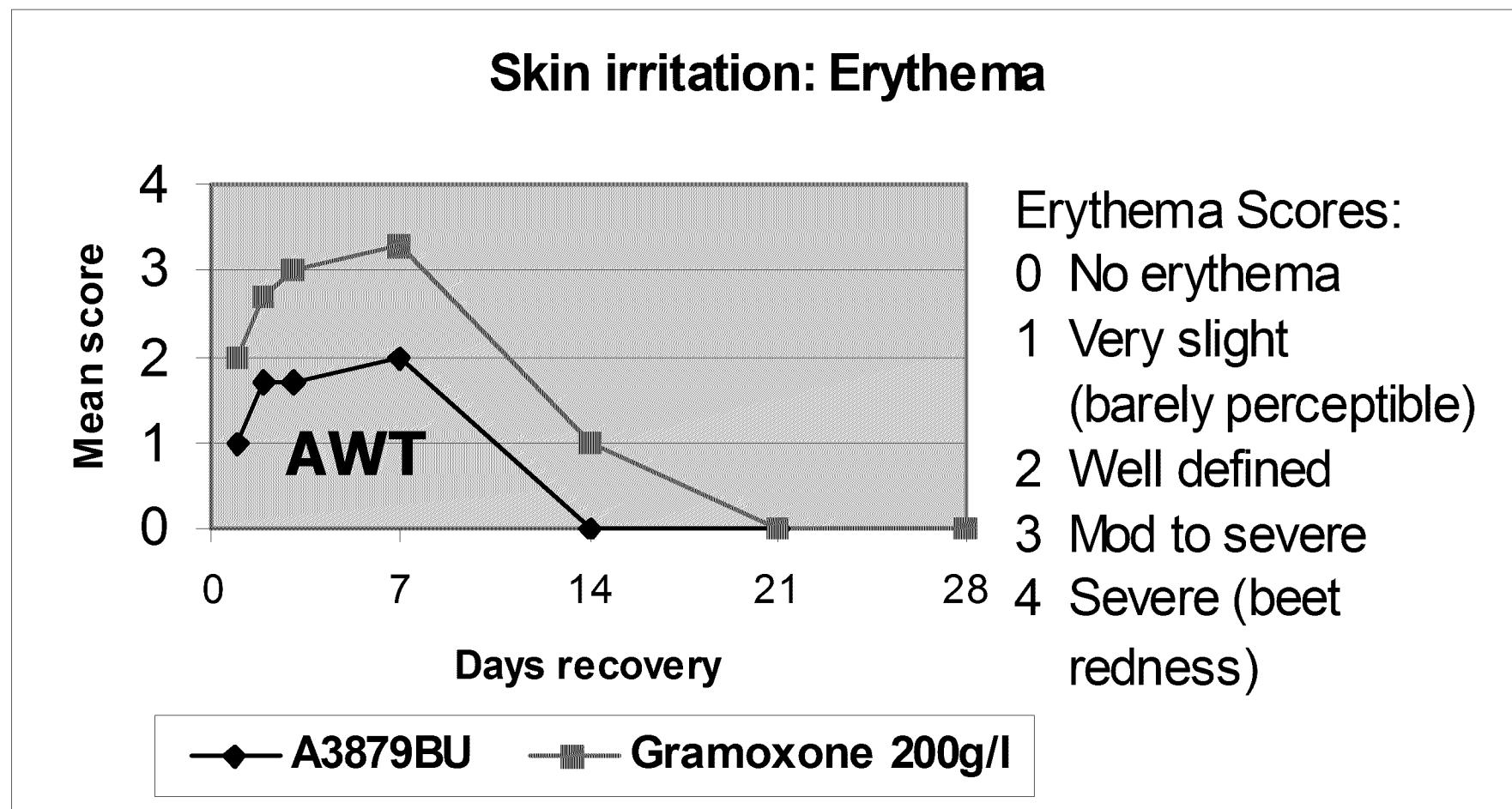
# Plasma emetic values following an oral dose of A3879BU (46 -736mg formulation/kg bwt.) in dogs (n = 3)



# Acute Oral Toxicity Summary

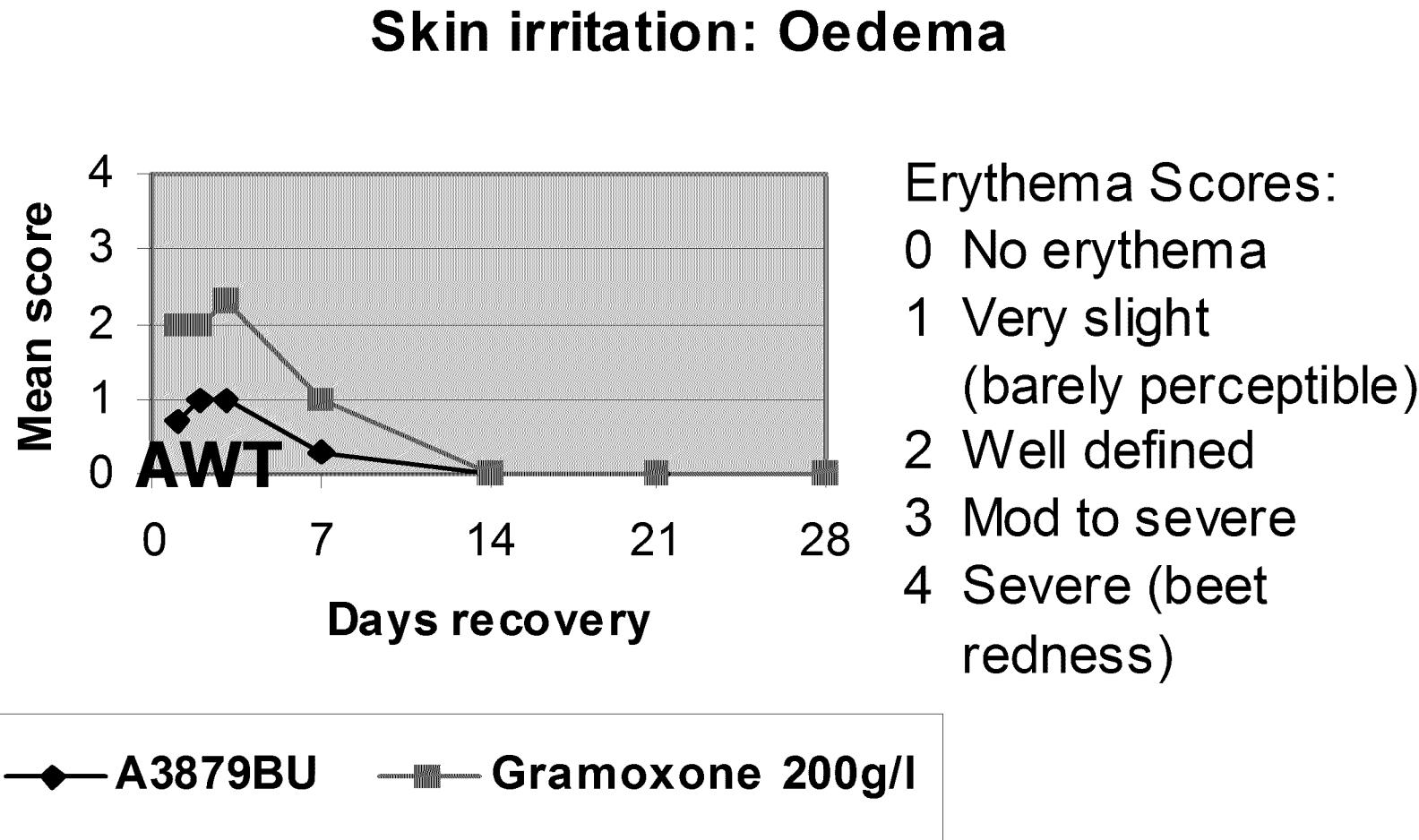
- **Significant reduction in absorption of paraquat in dog following oral ingestion**
- **Dogs tolerated 10 fold increase over known lethal dose**
- **Conservative estimate of a 5-fold safening for humans**
- **Essentially eliminating fatalities from accidental ingestion**

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



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

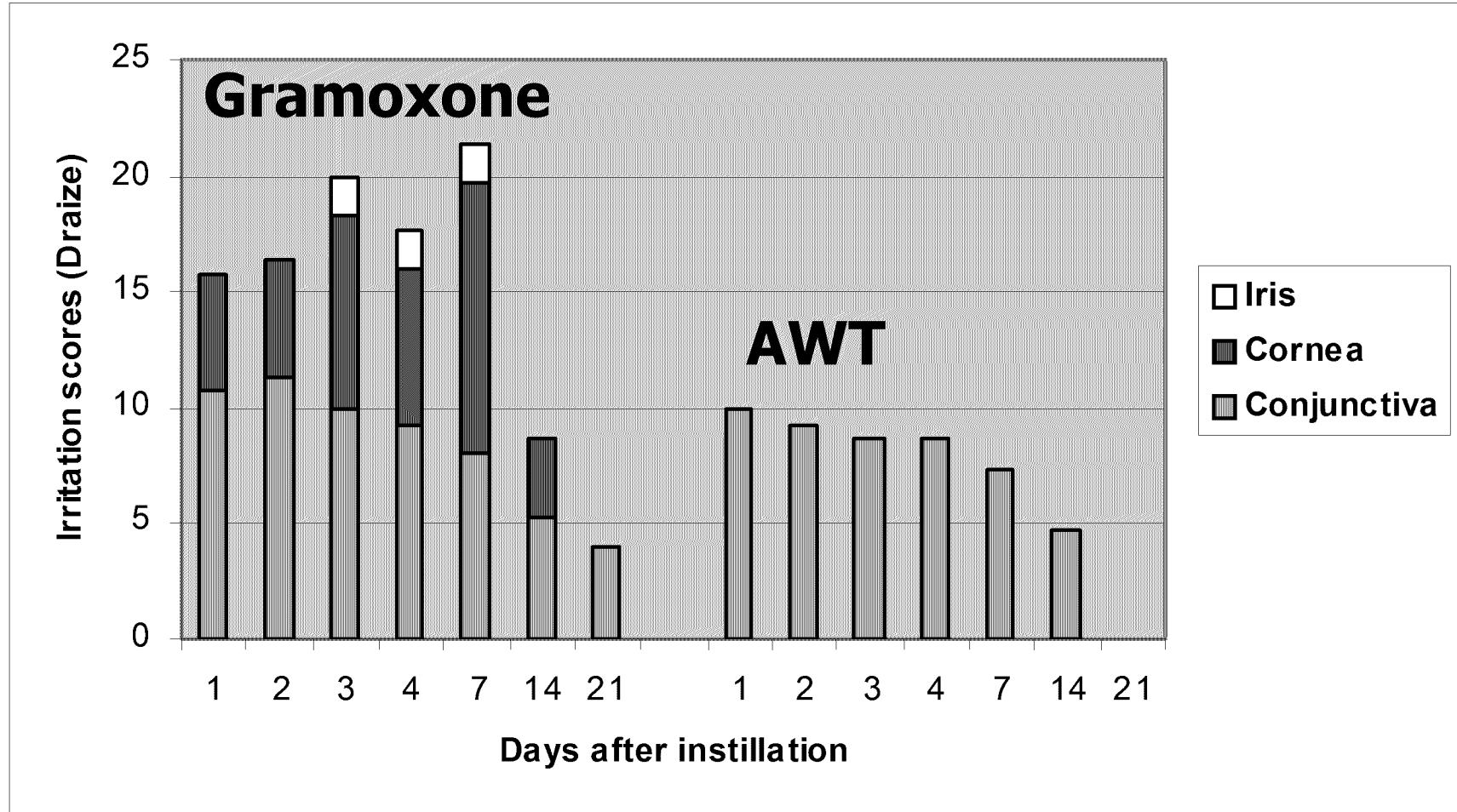


Gramoxone AW

**EPA Skin Irritation Category IV**  
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# Comparative eye irritancy – AWT 200 g/l and Gramoxone 200g/l formulations

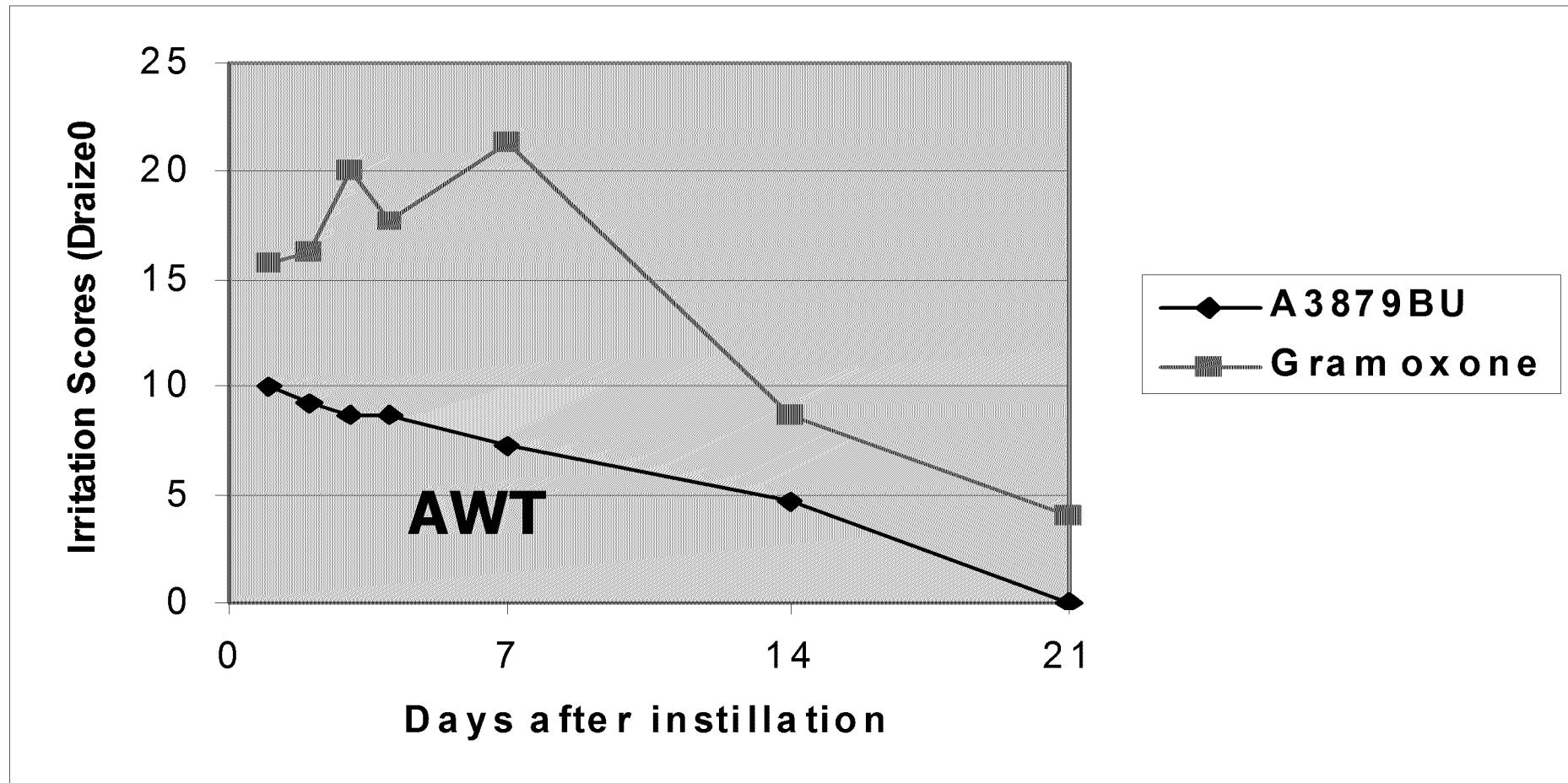


Gramoxone AW

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# Comparative eye irritancy – AWT 200 g/l and Gramoxone 200g/l formulations



Gramoxone AW

**Eye Irritation EPA Category II**  
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# **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**



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# Next Steps

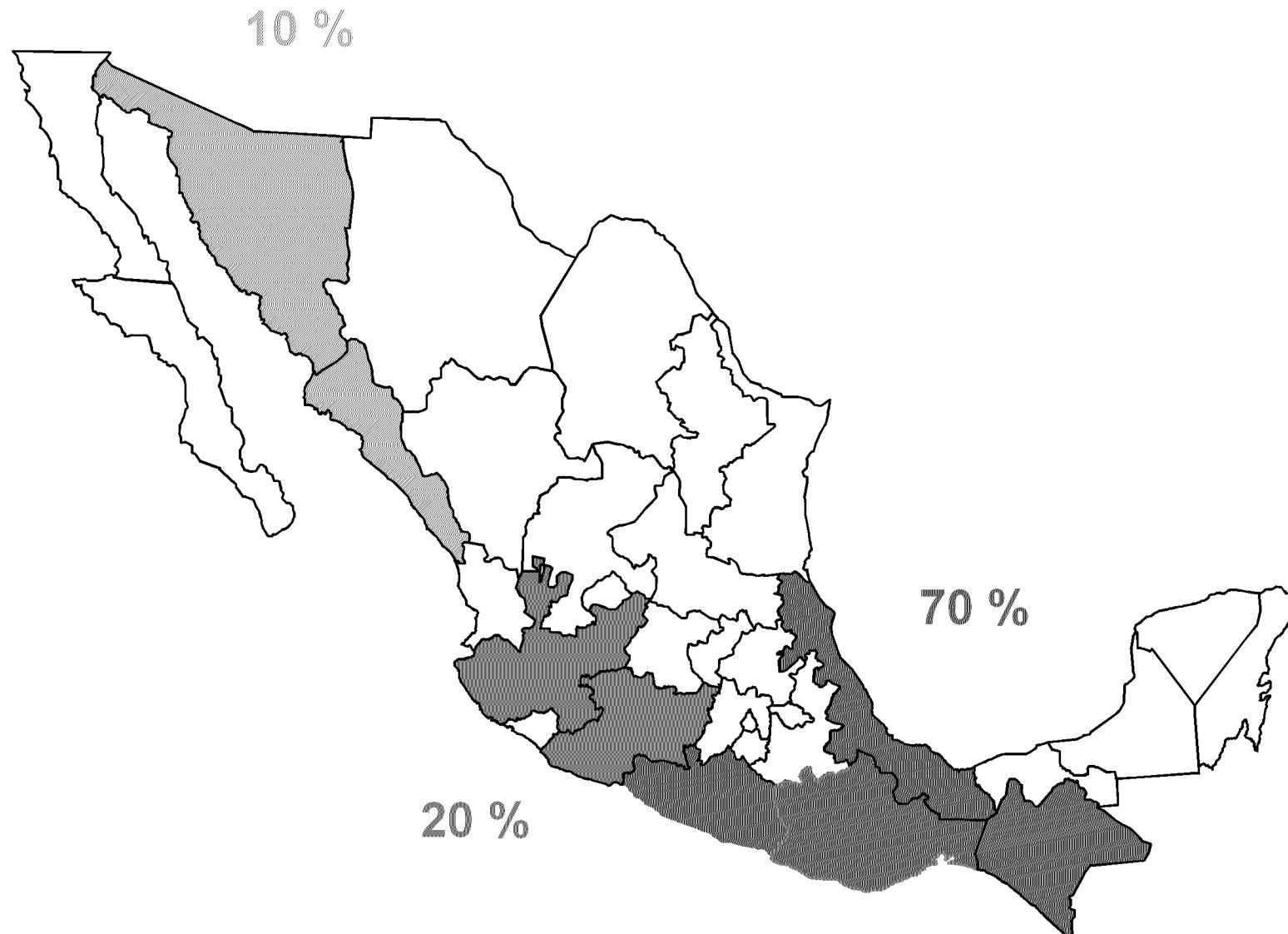
- Request Amendment of technical label / conditions of registration
- Submission of 200 g/l dog studies, overview of historical data
- Request 'Joint Review' process for NAFTA  
Will also discuss with CDPR
- Submission of 240 g/l acute toxicology, product chemistry studies, dog studies

# **Overview of Paraquat Use in Mexico**

**Maurilio Flores, R&D / Regulatory  
Director, Syngenta Mexico**



# Paraquat Use in Mexico



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**



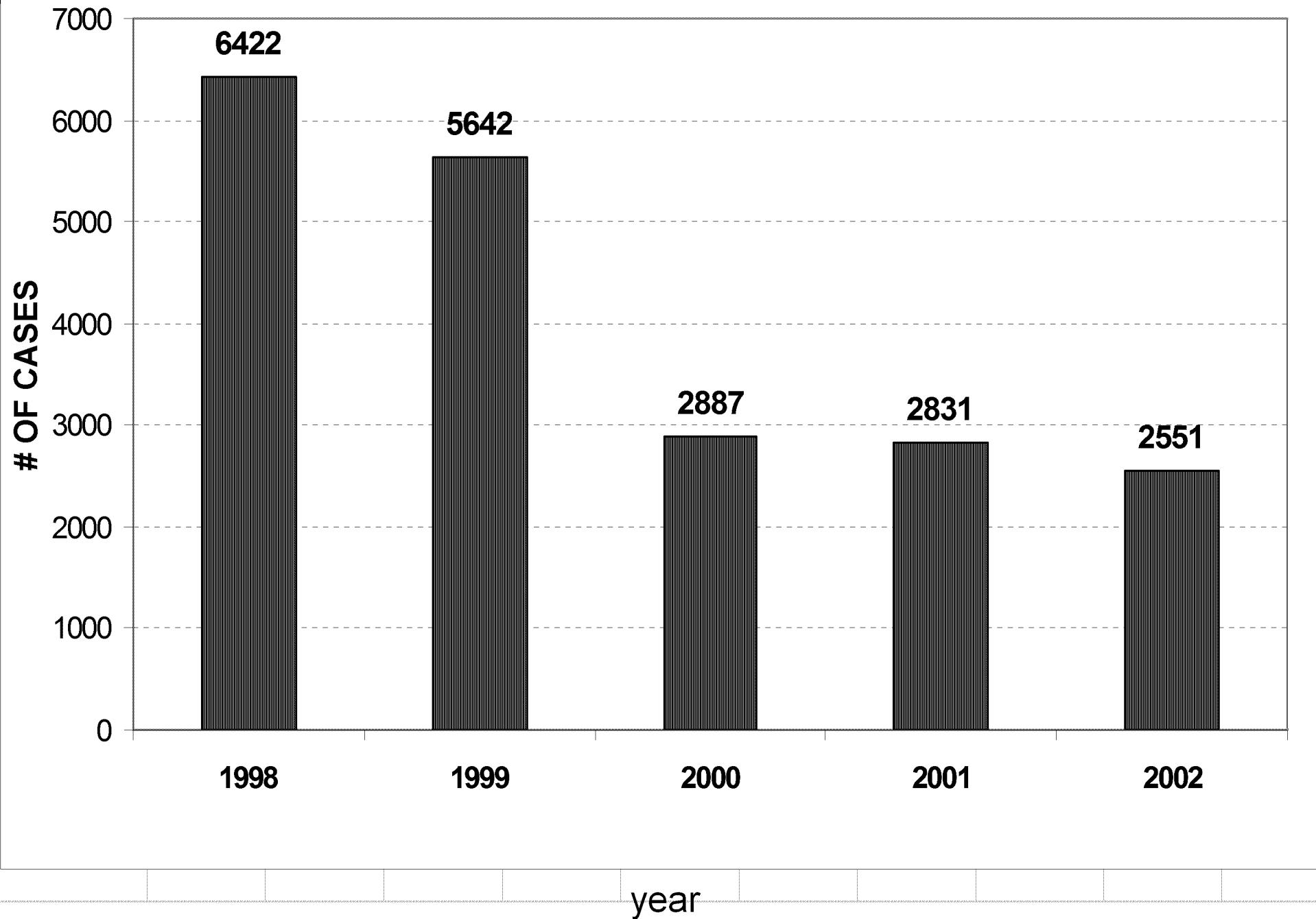
# How big is the issue in Mexico?

- **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**

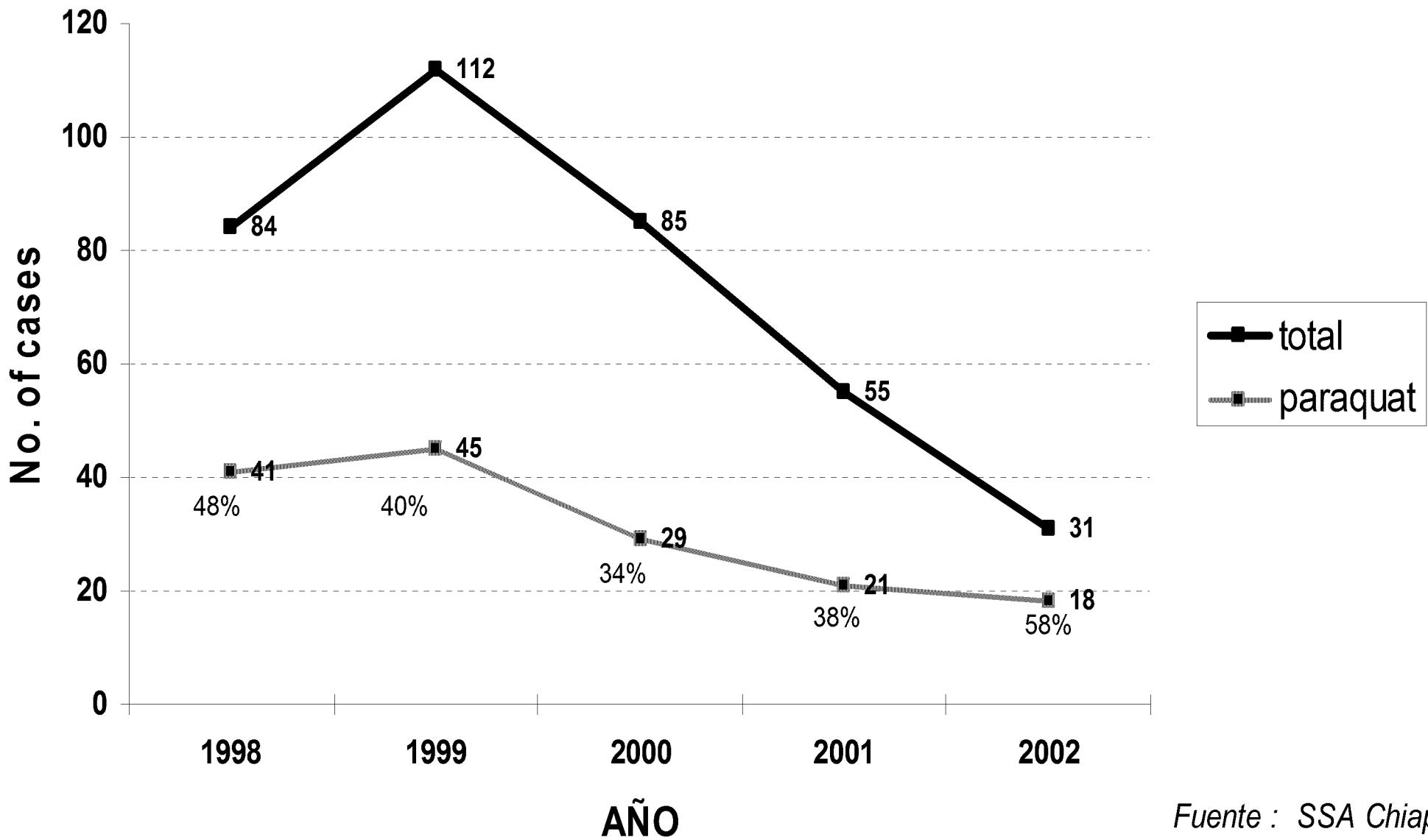
# Why Chiapas ?

- **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 )**



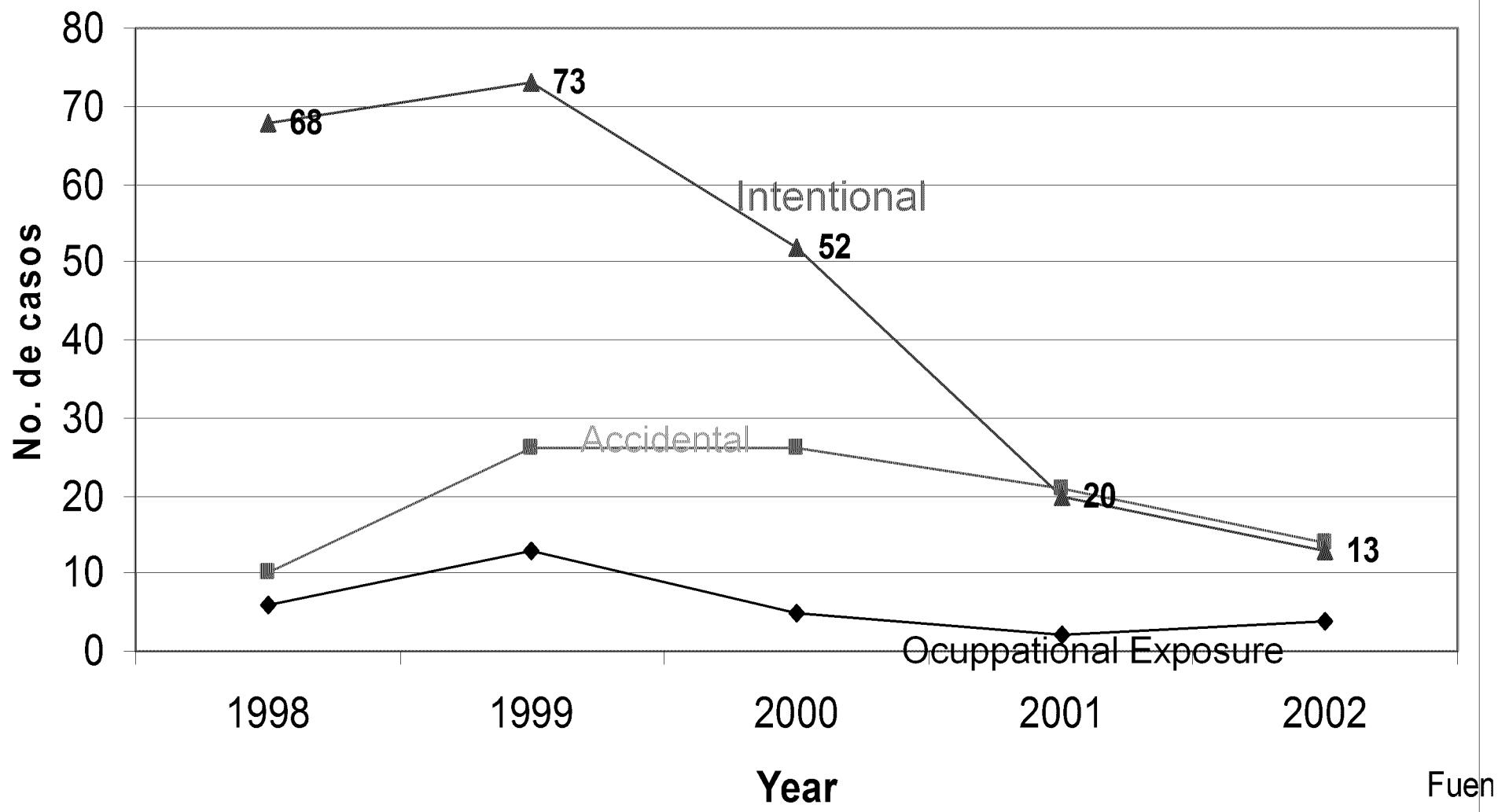
# Intoxications in the State of Chiapas



Fuente : SSA Chiapas

# Type of Intoxication

## All Pesticides, State of Chiapas





# LUPPA PROGRAM

## Syngenta México .... Since 1987



## LOS USOS PARA LOS PEQUEÑOS AGRICULTORES

# **Small Maize Grower – Low Level of Technology**

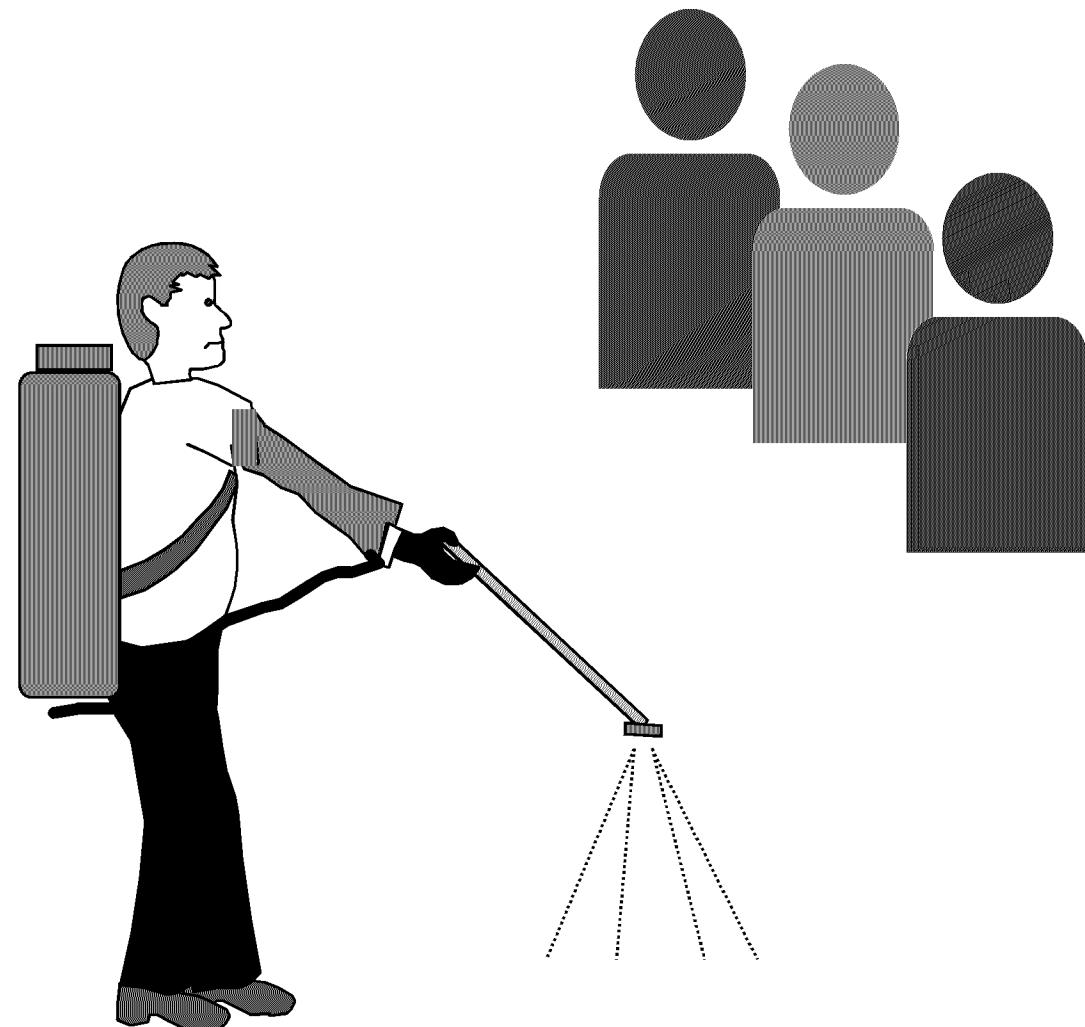


**started: 1987**

# PRESENTATIONS



# FIELD DEMO PLOTS





# RESULTS: 1987 - 2003

<b>Year</b>	<b>Presentat.</b>	<b>field demo plots</b>	<b>No. Farmers</b>
<b>1987</b>	45	45	2,400
<b>1988</b>	122	120	5,641
<b>1989</b>	160	137	8,347
<b>1990</b>	450	270	12,972
<b>1991</b>	1,785	659	54,241
<b>1992</b>	1,263	500	55,677
<b>1993</b>	1,643	978	64,455
<b>1994</b>	569	454	22,361
<b>1995</b>	433	392	49,257
<b>1996</b>	614	570	9,081
<b>1997</b>	1,141	784	39,377
<b>1998</b>	1,494	2,365	50,927
<b>1999</b>	1,745	1,654	13,903
<b>2000</b>	356	267	8,402
<b>2001</b>	402	379	10,180
<b>2002</b>	708	420	19,605
<b>2003</b>	491	188	11,175
<b>total</b>	<b>13,421</b>	<b>10,182</b>	<b>438,001</b>

# Historical Data - Gavage : Capsule Comparision

TABLE 3 – PLASMA PARAQUAT AREA UNDER CURVE

	Dose received		Method of administration	Paraquat AUC ( $\mu\text{g}/\text{ml.h}$ )		
	mg formulation/kg	Mg paraquat ion/kg		1h	4h	24h
Gramoxone	44	8	Capsule (n=12)	$2.21 \pm 0.22$	$10.06 \pm 0.49$	$15.98 \pm 0.89$
			Gavage (n=7)	$2.32 \pm 0.16$	$8.73 \pm 0.43$	$14.63 \pm 1.00$

