UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

November 29, 2004

MEMORANDUM

Subject:	Name of Pesticide Product:	Gramoxone Inteon	
	EPA File Symbol:	100-RERT	
	DP Barcode:	D309349	
	Decision No.:	348898	
	PC Code:	061601	Paraquat dichloride

From: Breann Hanson, Toxicologist
Technical Review Branch
Registration Division (7505C)

To: Hope Johnson, RM Team 25
Herbicide Branch
Registration Division (7505C)

Applicant: Syngenta Crop Protection, Inc.
P.O. Box 18300
Greensboro, NC 27419

FORMULATION FROM LABEL:

Active Ingredient:			% by wt.
061601	Paraquat dichloride	CAS No. 1910-42-5	30.1%
Inert Ingredients:			69.9%
		Total:	100.0%

ACTION REQUESTED:
The Product Manager requests:

(1)

"The registrant, Syngenta, has submitted an application for a new formulation of paraquat dichloride. The formulation is designed to gel if ingested, thus minimizing entry to intestine. They have submitted the five pack of acute tox (inhalation study is cited, and i have blown back a copy for your review), along with toxicokinetic study in the dog to show how the gelling effect helps lessen the toxicity. Please review these studies for acceptance. This product is a me-too with 100-1009, so please review to see if this product is toxicologically substantially similar to 100-1009 cyclone. I have included MRID's 46364503-46364518, along with the CSF, the application letter, the data matrix, the label, and the me-too label and csf for comparison. NOTE: MRID's 46364511-46364518 are for the 200 g/l formulation that will be used in Mexico. The 240 g/l formulation will be used here in the U.S. However, Jim Jones agreed to review the Mexican formulation studies for Mexico under the NAFTA Agreement. For further information, contact Luis Suguiyama 305-6027..."

BACKGROUND: Syngenta Crop Protection, Inc. has submitted 2 sets of 5 pack acute toxicity studies in support of registration for Gramoxone Inteon, EPA File Symbol: 100-RERT. The submission included a CSF, label, application, data matrx and letter from the sponsor. The studies were conducted at SafePharm Laboratories Ltd., Derbyshire, UK (MRID numbers 463645-03 through -06), Product Safety Laboratories, Dayton, NJ (MRID number 463645-07), or Central Toxicology Laboratory, Cheshire, UK (MRID numbers 463645-12 through -16). Two of the submitted studies (MRIDs 463645-08 and -09) will not be reviewed by TRB due to be being extraneous to this registration. The 4 toxicokinetic studies have been forwarded to HED. No acute inhalation toxicity study was submitted due to the fact that the company has agreed to take a category I classification for the inhalation route.

RECOMMENDATIONS: The studies have been reviewed and are classified as acceptable. Because actual studies have been submitted no determination of similarity with 100-1009 has been made. The acute toxicity profile for the 240 g/L Gramoxone Inteon formulation, EPA File Symbol: 100-RERT, is:

Acute oral toxicity	II	Acceptable	MRID 46364503
Acute dermal toxicity	II	Acceptable	MRID 46364514*
Acute inhalation toxicity	I	Cited	MRID 00046105
Primary eye irritation	II	Acceptable	MRID 46364506
Primary skin irritation	III	Acceptable	MRID 46364504
Dermal sensitization	Negative	Acceptable	MRID 46364507

* although a study (MRID 46364505) was submitted for the 240 g/L formulation in which the category for acute dermal toxicity is III, the study sent in for the 200 g/L formulation has a more restrictive category II for dermal toxicity. It is TRB's recommendation that this more restrictive study be used to register the 240 g/L formulation. The signal word remains DANGER.

(2)

LABELING: Based on the toxicity profile above, the following are the precautionary and first aid statements for this product as obtained from the Label Review System:

PRODUCT ID #: **000100-01217**

PRODUCT NAME: Gramoxone Inteon

PRECAUTIONARY STATEMENTS

Hazards to Humans and Domestic Animals:

SIGNAL WORD: DANGER **POISON** ☠

SPANISH SIGNAL WORD: PELIGRO
Si usted no entiende la etiqueta, busque a alguien para que se la explique a usted en detalle.
(If you do not understand the label, find someone to explain it to you in detail.)

Restricted Use Pesticide due to toxicity categories. For retail sale to and use only by Certified Applicators or persons under their direct supervision and only for those uses covered by the Certified Applicator's certification.

Fatal if inhaled. Do not breathe spray mist. May be fatal if swallowed or absorbed through skin. Causes substantial but temporary eye injury. Do not get in eyes, on skin, or on clothing. Wear protective eyewear (goggles, face shield, or safety glasses). Wear coveralls worn over short-sleeved shirt and short pants, socks, chemical resistant footwear, and chemical-resistant gloves (such as Natural Rubber, Selection Category A).

For handling activities, use a non-powered, NIOSH-approved air purifying cartridge respirator equipped with an organic-vapor (OV) removing cartridge plus an N-, R- or P-series filter, OR a non-powered air purifying canister-type respirator equipped with an organic vapor canister that uses an N-, R-, or P-series air-purifying filter.

USER SAFETY RECOMMENDATIONS:
Remove and wash contaminated clothing before reuse. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, or using tobacco.

First Aid:

If inhaled:
-Move the person to fresh air.
-If person is not breathing, call 911 or an ambulance, then give artificial respiration, preferably mouth-to-mouth if possible.
-Call a poison control center or doctor for further treatment advice.

If swallowed:
-Call a poison control center or doctor immediately for treatment advice.
-Have person sip a glass of water if able to swallow.
-Do not induce vomiting unless told to by a poison control center or doctor.
-Do not give anything to an unconscious person.

If in eyes:
-Hold eye open and rinse slowly and gently with water for 15-20 minutes.
-Remove contact lenses, if present, after the first 5 minutes, then continue rinsing.
-Call a poison control center or doctor for treatment advice.

If on skin:
-Take off contaminated clothing.
-Rinse skin immediately with plenty of water for 15-20 minutes.
-Call a poison control center or doctor for treatment advice.

NOTE TO PHYSICIAN: Note to PM/CRM/Registrant: The proposed label should contain a Note to Physician which addresses the category I Acute Inhalation Toxicity. The following statements are suggested types of information that may be included, if applicable:
- technical information on symptomatology;
- use of supportive treatments to maintain life functions;
- medicine that will counteract the specific physiological effects of the pesticide;
- company telephone number to specific medical personnel who can provide specialized medical advice.

Have the product container or label with you when calling a poison control center or doctor or going for treatment. You may also contact 1-800-xxx-xxxx for emergency medical treatment information.

The acute toxicity profile for the 200 g/L Gramoxone Inteon formulation, EPA File Symbol: 100-RERT, is:

Acute oral toxicity	III	Acceptable	MRID 46364515
Acute dermal toxicity	II	Acceptable	MRID 46364514
Acute inhalation toxicity	I	Cited	MRID 00046105
Primary eye irritation	II	Acceptable	MRID 46364512
Primary skin irritation	IV	Acceptable	MRID 46364513
Dermal sensitization	Negative	Acceptable	MRID 46364516

LABELING: Based on the toxicity profile above, the following are the precautionary and first aid statements for this product as obtained from the Label Review System:

PRODUCT ID #: **000100-01217**

PRODUCT NAME: Gramoxone Inteon

PRECAUTIONARY STATEMENTS

Hazards to Humans and Domestic Animals:

SIGNAL WORD: DANGER **POISON** ☠

SPANISH SIGNAL WORD: PELIGRO
Si usted no entiende la etiqueta, busque a alguien para que se la explique a usted en detalle.
(If you do not understand the label, find someone to explain it to you in detail.)

Restricted Use Pesticide due to toxicity categories. For retail sale to and use only by Certified Applicators or persons under their direct supervision and only for those uses covered by the Certified Applicator's certification.

Fatal if inhaled. Do not breathe spray mist. May be fatal if absorbed through skin. Causes substantial but temporary eye injury. Harmful if swallowed. Do not get in eyes, on skin, or on clothing. Wear coveralls worn over long-sleeved shirt and long pants, socks, chemical-resistant footwear, and chemical-resistant gloves (such as Natural Rubber, Selection Category A). Wear protective eyewear (goggles, face shield, or safety glasses).

For handling activities, use a non-powered, NIOSH-approved air purifying cartridge respirator equipped with an organic-vapor (OV) removing cartridge plus an N-, R- or P-series filter, OR a non-powered air purifying canister-type respirator equipped with an organic vapor canister that uses an N-, R-, or P-series air-purifying filter.

Follow the manufacturer's instructions for cleaning/maintaining PPE. If no such instructions for washables, use detergent and hot water. Keep and wash PPE separately from other laundry. When mixing and loading wear a chemical resistant apron. For overhead exposure wear chemical-resistant headgear. When cleaning equipment wear a chemical-resistant apron.

USER SAFETY RECOMMENDATIONS:
Remove and wash contaminated clothing before reuse. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, or using tobacco.

First Aid:

If inhaled:
-Move the person to fresh air.
-If person is not breathing, call 911 or an ambulance, then give artificial respiration, preferably mouth-to-mouth if possible.
-Call a poison control center or doctor for further treatment advice.

If on skin:
-Take off contaminated clothing.
-Rinse skin immediately with plenty of water for 15-20 minutes.
-Call a poison control center or doctor for treatment advice.

If in eyes:
-Hold eye open and rinse slowly and gently with water for 15-20 minutes.
-Remove contact lenses, if present, after the first 5 minutes, then continue rinsing.
-Call a poison control center or doctor for treatment advice.

If swallowed:
-Call a poison control center or doctor immediately for treatment advice.
-Have person sip a glass of water if able to swallow.
-Do not induce vomiting unless told to by a poison control center or doctor.
-Do not give anything to an unconscious person.

NOTE TO PHYSICIAN: Note to PM/CRM/Registrant: The proposed label should contain a Note to Physician which addresses the category I Acute Inhalation Toxicity. The following statements are suggested types of information that may be included, if applicable:
- technical information on symptomatology;
- use of supportive treatments to maintain life functions;
- medicine that will counteract the specific physiological effects of the pesticide;
- company telephone number to specific medical personnel who can provide specialized medical advice.

Have the product container or label with you when calling a poison control center or doctor or going for treatment. You may also contact 1-800-xxx-xxxx for emergency medical treatment information.

Reviewer: Breann Hanson **Date:** Nov. 29, 2004
Risk Manager (EPA): Hope Johnson, RM 25

STUDY TYPE: Acute Oral Toxicity - SD rat; OPPTS 870.1100; OECD 425

TEST MATERIAL: Paraquat 240 g/l SL Formulation (A7813K) (Paraquat: 22.3%, Batch Reference: J4267/75-2; green liquid)

CITATION: Pooles, A. (2004) Paraquat 240 g/l SL Formulation (A7813K): Acute Oral Toxicity in the Rat. Laboratory Study Identification: 006/438. Unpublished study prepared by SafePharm Laboratories Ltd. August 3, 2004. MRID 46364503.

SPONSOR: Syngenta Crop Protection, Inc., P.O. Box 18300, Greensboro, NC 27419

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 46364503), 6 female Sprague-Dawley rats (Age: 8-12 weeks, Weight: 203-234 g; Source: Charles River (UK) Ltd., Kent, UK) were given a single oral dose of Paraquat 240 g/l SL Formulation (A7813K) (Paraquat: 22.3%, Batch Reference: J4267/75-2; green liquid) by oral gavage. The study was initiated at a dose of 175 mg/kg in one female, and due to survival of that animal an additional 5 females were dosed at either 175 or 550 mg/kg following the up-and-down procedure. Individual animal body weights were recorded prior to test substance administration and again on days 7 and 14, or at death. Clinical checks for mortality and signs of toxicity were made four times post-dosing on initial study day and at least once daily for 14 days. All animals were necropsied on study day 14.

The 3 animals dosed at 175 mg/kg survived, gained weight and appeared healthy throughout the study. No gross internal findings were observed at necropsy.

The 3 animals dosed at 550 mg/kg died by study day 4. One animals was killed *in extremis* on study day 3. Signs of toxicity noted in 2/3 animals included hunched posture, piloerection and laboured respiration and/or decreased respiratory rate. Lethargy and ataxia were also noted in one animal, as well as emaciation. At necropsy, animals that died during the study were noted as having abnormally red lungs, dark liver and dark kidneys. No gross internal findings were observed for the animal killed *in extremis*.

Oral LD_{50} Females = 310 mg/kg (95% C.I.= 175-550 mg/kg)

Based on the LD_{50} in female rats, Paraquat 240 g/l SL Formulation (A7813K) is classified as EPA Toxicity Category II.

This acute oral study is classified as acceptable. It does satisfy the guideline requirement for an acute oral study (OPPTS 870.1100; OECD 425) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Individual animals were dosed as follows:

Main Test

Dosing Sequence	Animal No.	Sex	Dose level (mg/kg)	Sort-Term Outcome	Long-Term Outcome
1	1-0	F	175	S	S
2	2-0		550	D	D
3	3-0		175	S	S
4	4-0		550	D	D
5	5-0		175	S	S
6	6-0		550	D	D

S = survival D = death

AOT425statpgm (Version: 1.0) Test Results and Recommendations
Acute Oral Toxicity (OECD Test Guideline 425) Statistical Program
Date/Time: Tuesday, November 23, 2004, 12:55:41 PM
Data file name: work.dat
Last modified: 11/23/2004 12:55:41 PM

Test/Substance: paraquat
Test type: Main Test
Limit dose (mg/kg): 5000
Assumed LD50 (mg/kg): Default
Assumed sigma (mg/kg): 0.5

Recommended dose progression: 5000, 1750, 550, 175, 55, 17.5, 5.5, 1.75

DATA:

8

Test Seq.	Animal ID	Dose (mg/kg)	Short-term Result	Long-term Result
1	1-0	175	O	O
2	2-0	550	X	X
3	3-0	175	O	O
4	4-0	550	X	X
5	5-0	175	O	O
6	6-0	550	X	X

(X = Died, O = Survived)

Dose Recommendation: The main test is complete.
Stopping criteria met: 5 reversals in 6 tests. LR criterion.

SUMMARY OF LONG-TERM RESULTS:

Dose	O	X	Total
175	3	0	3
550	0	3	3
All Doses	3	3	6

Statistical Estimate based on long term outcomes:
Estimated LD50 = 310.2 (Based on an assumed sigma of 0.5).
Approximate 95% confidence interval is 175 to 550.

A. Mortality - As noted in table.

B. Clinical observations - The 3 animals dosed at 175 mg/kg survived, gained weight and appeared healthy throughout the study.

The 3 animals dosed at 550 mg/kg died by study day 4. One animals was killed *in extremis* on study day 3. Signs of toxicity noted in 2/3 animals included hunched posture, piloerection and laboured respiration and/or decreased respiratory rate. Lethargy and ataxia were also noted in one animal, as well as emaciation.

C. Gross Necropsy - No gross internal findings were observed at necropsy for the animals surviving the study or the one animal killed *in extremis*.

Findings at necropsy for the remaining animals included abnormally red lungs, dark liver and dark kidneys.

D. Reviewer's Conclusions: Agree with study author.

Reviewer: Breann Hanson **Date:** Nov. 29, 2004

Risk Manager (EPA): Hope Johnson, RM 25

STUDY TYPE: Acute Dermal Toxicity - SD Rat; OPPTS 870.1200; OECD 402

TEST MATERIAL: Paraquat 240 g/l SL Formulation (A7813K) (Paraquat: 22.3%, Batch Reference: J4267/75-2; green liquid)

CITATION: Pooles, A. (2004) Paraquat 240 g/l SL Formulation (A7813K): Acute Dermal Toxicity (Limit Test) in the Rat. Laboratory Study Identification: 006/439. Unpublished study prepared by SafePharm Laboratories Ltd. August 3, 2004. MRID 46364505.

SPONSOR: Syngenta Crop Protection, Inc., P.O. Box 18300, Greensboro, NC 27419

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 46364505), 5/sex of Sprague-Dawley rats (Age: 8-12 weeks; Weight: 238-268 g males, 208-224 g females; Source: Charles River (UK) Ltd., Kent, UK) were dermally exposed to a single application of Paraquat 240 g/l SL Formulation (A7813K) (Paraquat: 22.3%, Batch Reference: J4267/75-2; green liquid) at 2,000 mg/kg. At first only 2 animals were treated (1 male, 1 female). Afterwards an additional 8 animals were treated. The test material was applied evenly to each exposure area, approximately 10% of the total BSA, covered with gauze and then semi-occluded with self-adhesive bandages for 24 hours. Individual animal body weights were recorded prior to test substance administration and again on days 7 and 14, or after death. Clinical checks for mortality and signs of toxicity were made four times post-application on initial study day and at least once daily for 14 days. Animals were also graded for dermal irritation (Draize) after removal of the dressings and once daily for 14 days. All animals were necropsied on study day 14.

2/5 females were killed *in extremis* during the study. All remaining animals survived the study. Survivors gained weight throughout the study, except for 2 females which lost weight during the first week of the study. Signs of toxicity noted in females included hunched posture, lethargy, ataxia, decreased respiratory rate, laboured or increased respiration, dehydration, emaciation, pallor of the extremities and red/brown staining around the snout and eyes. Females recovered from these symptoms by study day 12. Males appeared normal throughout the study. Dermal irritation noted during the study included well-defined erythema, crust formation and hardened light brown-coloured scabs, small superficial scattered scabs and glossy skin. At necropsy, abnormally red lungs were noted in one of the females killed *in extremis*. No gross internal findings were observed at necropsy for the remaining animals.

Dermal LD_{50} Males => 2,000 mg/kg
Females => 2,000 mg/kg
Combined => 2,000 mg/kg

Based on the dermal LD_{50} of 2,000 mg/kg, Paraquat 240 g/l SL Formulation (A7813K) is classified as EPA Toxicity Category III.

This acute dermal study is classified acceptable. It does satisfy the guideline requirement for an acute dermal study (OPPTS 870.1200; OECD 402) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Dose (mg/kg)	Mortality/Number Tested		
	Males	Females	Combined
2000	0/5	2/5	2/10

A. Mortality - As noted in table.

B. Clinical observations - 2/5 females were killed *in extremis* during the study. All remaining animals survived the study. Survivors gained weight throughout the study, except for 2 females which lost weight during the first week of the study. Signs of toxicity noted in females included hunched posture, lethargy, ataxia, decreased respiratory rate, laboured or increased respiration, dehydration, emaciation, pallor of the extremities and red/brown staining around the snout and eyes. Females recovered from these symptoms by study day 12. Males appeared normal throughout the study. Dermal irritation noted during the study included well-defined erythema, crust formation and hardened light brown-coloured scabs, small superficial scattered scabs and glossy skin.

C. Gross Necropsy - At necropsy, abnormally red lungs were noted in one of the females killed *in extremis*. No gross internal findings were observed at necropsy for the remaining animals.

D. Reviewer's Conclusions: Agree with study author.

Reviewer: Breann Hanson **Date:** Nov. 29, 2004

Risk Manager (EPA): Hope Johnson, RM 25

STUDY TYPE: Primary Eye Irritation - NZW Rabbit, OPPTS 870.2400; OECD 405

TEST MATERIAL: Paraquat 240 g/l SL Formulation (A7813K) (Paraquat: 22.3%, Batch Reference: J4267/75-2; green liquid)

CITATION: Pooles, A. (2004) Paraquat 240 g/l SL Formulation (A7813K): Acute Eye Irritation in The Rabbits. Laboratory Study Identification: 006/407. Unpublished study prepared by SafePharm Laboratories Ltd. July 14, 2004. MRID 46364506.

SPONSOR: Syngenta Crop Protection, Inc., P.O. Box 18300, Greensboro, NC 27419

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 46364506), 0.1 mL of undiluted Paraquat 240 g/l SL Formulation (A7813K) (Paraquat: 22.3%, Batch Reference: J4267/75-2; green liquid) was instilled into the conjunctival sac of the right eye of 3 male young adult New Zealand albino rabbits (Source: David Percival Ltd., Cheshire, UK). The untreated left eye served as a control. At first only one animal was treated and an assessment of the initial pain reaction was made. The two remaining animals were given one drop of local anaesthetic into both eyes prior to instillation. Animals were then observed at 1, 24, 48, 72 hours and on days 7, 10, 14, 17, 21 and for two treated eyes on days 24 and 28, post-instillation. Irritation was scored according to Draize.

No corneal opacity or iritis was noted at any point during the study. One hour after instillation 3/3 eyes exhibited conjunctivitis redness, chemosis and discharge (scores 1-2). Positive effects were noted in 2/3 eyes through study day 10. 1 eye experienced positive discharge (score 2) through study day 24. 1 treated eye exhibited an area of haemorrhage over the nictitating membrane at 24-hours. Haemorrhaging was noted in all treated eyes at 48 and 72-hours. Fur loss around the treated eye was noted in 3/3 treated eyes on study days 10, 14 and 17, with this loss persisting in one eye to the 21-day observation.

The test substance is mildly irritating. In this study, Paraquat 240 g/l SL Formulation (A7813K) is classified as EPA Toxicity Category II.

This study is classified as acceptable. It does satisfy the guideline requirement for a primary eye irritation study (OPPTS 870.2400; OECD 405) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS AND DISCUSSION:

Observations	Number "positive"/number tested										
	Hours				Days						
	1	24	48	72	7	10	14	17	21	24	28
Corneal Opacity	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
Iritis	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
Conjunctivae											
Redness*	3/3	3/3	3/3	3/3	3/3	1/3	0/3	0/3	0/3	0/3	0/3
Chemosis*	1/3	1/3	2/3	1/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
Discharge*	0/3	3/3	3/3	3/3	3/3	2/3	1/3	1/3	1/3	1/3	0/3

*Score of 2 or more required to be considered "positive"

A. Observations - No corneal opacity or iritis was noted at any point during the study. One hour after instillation 3/3 eyes exhibited conjunctivitis redness, chemosis and discharge (scores 1-2). Positive effects were noted in 2/3 eyes through study day 10. 1 eye experienced positive discharge (score 2) through study day 24. 1 treated eye exhibited an area of haemorrhage over the nictitating membrane at 24-hours. Haemorrhaging was noted in all treated eyes at 48 and 72-hours. Fur loss around the treated eye was noted in 3/3 treated eyes on study days 10, 14 and 17, with this loss persisting in one eye to the 21-day observation.

B. Reviewer's Conclusions: Agree with the study author.

Reviewer: Breann Hanson **Date:** Nov. 29, 2004
Risk Manager (EPA): Hope Johnson, RM 25

STUDY TYPE: Primary Dermal Irritation - NZW Rabbit; OPPTS 870.2500; OECD 404

TEST MATERIAL: Paraquat 240 g/l SL Formulation (A7813K) (Paraquat: 22.3%, Batch Reference: J4267/75-2; green liquid)

CITATION: Pooles, A. (2004) Paraquat 240 g/l SL Formulation (A7813K): Acute Dermal Irritation In The Rabbit. Laboratory Study Identification: 006/406. Unpublished study prepared by SafePharm Laboratories Ltd. July 13, 2004. MRID 46364504.

SPONSOR: Syngenta Crop Protection, Inc., P.O. Box 18300, Greensboro, NC 27419

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 46364504), 3 young adult New Zealand albino rabbits (1 male, 2 females; Source: David Percival Ltd., Cheshire, UK) were dermally exposed to 0.5 mL of undiluted Paraquat 240 g/l SL Formulation (A7813K) (Paraquat: 22.3%, Batch Reference: J4267/75-2; green liquid). Initially only one animal was treated and after consideration of the skin reactions in this animal two additional animals were treated. The test substance was introduced under a gauze patch, placed on the dose site on each animal and then secured with a strip of surgical adhesive tape for 4 hours. Animals were then observed for up to 28 days, to assess the reversibility of skin reactions.. Dermal irritation was scored according to the Draize system at 1, 24, 48, 72 hours post-patch removal for all animals and up through study days 7, 10, 14, 17, 21, 24 and 28.

One hour post-patch removal well-defined erythema (score 2) and very slight oedema (score 1) was noted at 2/3 treated sites. This irritation persisted at 72 hours for both treated sites, persisting to the 7-day observation in one animal. Very slight erythema (score 1) was noted at the other treated site from 24-hours to study day 14. One animal had extreme weight loss at the 72-hour observation and was killed for humane reasons. One skin site appeared normal at the 21-day observation while the other site appeared normal on study day 28.

Increased salivation, loss of skin elasticity, crust formation, reduced regrowth of fur, loss of skin flexibility and slight desquamation were also noted during the study.

In this study, the formulation is moderately irritating to the skin. Paraquat 240 g/l SL Formulation (A7813K) is classified as EPA Toxicity Category III.

This study is classified as acceptable. It does satisfy the guideline requirement for a primary dermal irritation study (OPPTS 870.2500; OECD 404) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

INDIVIDUAL SKIN IRRITATION SCORES

ERYTHEMA/EDEMA

Animal Number	Sex	Hours				Days						
		1	24	48	72	7	10	14	17	21	24	28
91	**M**	0/0	1/0	1/0	1/0	1/0	1/0	1/0	0/0	0/0	0/0	0/0
30[a]	**F**	2/1	2/1	2/1	2/1	-	-	-	-	-	-	-
31		2/1	2/1	2/2	2/2	2/2	-[b]	0/0	0/0	0/0	0/0	0/0
Severity of Irritation - Mean Score		1.3/ 0.6	1.6/ 0.6	1.6/ 1.0	1.6/ 1.0	1.5/ 1.0	1/0	0.5/ 0	0/0	0/0	0/0	0/0

[a] Animal 30 was killed for humane reasons after the 72-hour observation period.
[b] A reading for erythema and oedema could not be made to crust formation.

A. <u>Observations</u> - One hour post-patch removal well-defined erythema (score 2) and very slight oedema (score 1) was noted at 2/3 treated sites. This irritation persisted at 72 hours for both treated sites, persisting to the 7-day observation in one animal. Very slight erythema (score 1) was noted at the other treated site from 24-hours to study day 14. One animal had extreme weight loss at the 72-hour observation and was killed for humane reasons. One skin site appeared normal at the 21-day observation while the other site appeared normal on study day 28.

B. <u>Results</u> - Test substance is moderately irritating to the skin.

C. <u>Reviewer's Conclusions</u> - Agree with study author.

Reviewer: Breann Hanson **Date:** Nov. 29, 2004
Risk Manager (EPA): Hope Johnson, RM 25

STUDY TYPE: Dermal Sensitization - Guinea Pig; OPPTS 870.2600; OECD 406

TEST MATERIAL: Paraquat (240 g/L) and PP796 (1.5 g/L) SL (A7813K) (Paraquat: 22.3% w/w, Batch Reference: J4267/75-2; clear green liquid)

CITATION: Merkel, D. (2004) Dermal Sensitization Study in Guinea Pigs (Buehler Method) with Paraquat (240 g/L) and PP796 (1.5 g/L) SL (A7813K). Laboratory Study Identification: 15409. Unpublished study prepared by Product Safety Laboratories. July 23, 2004. MRID 46364507.

SPONSOR: Syngenta Crop Protection, Inc., P.O. Box 18300, Greensboro, NC 27419

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 46364507) with Paraquat (240 g/L) and PP796 (1.5 g/L) SL (A7813K) (Paraquat: 22.3% w/w, Batch Reference: J4267/75-2; clear green liquid), 30 male young adult Hartley guinea pigs (Weight: 382-480 g males; Source: Elm Hill Breeding Labs, Chelmsford, MA) were tested using the Buehler method. Once a week for 3 weeks, 0.4 mL of a 10% w/w mixture of the test substance in distilled water was applied to the dose site of each animal using a lint patch and secured with surgical tape to 20 test animals. After 6 hours of exposure, the patches were removed. 24 and 48 hours after each induction the animals were scored for dermal irritation. Thirteen days after the last induction dose challenge doses of 0.2 mL of a 1% w/w mixture of the test substance in distilled water and a 0.3% w/w mixture were applied to the right side of the test animals and to a set of 10 naive control guinea pigs for 6 hours. Approximately 24 and 48 hours after challenge, the animals were graded for dermal irritation. The procedures were validated using alpha-Hexylcinnamaldehyde (HCA) as the positive control substance.

All animals survived and appeared healthy throughout the study. During the induction phase of the study, very faint to faint erythema (score 0.5-1) was noted for most of the treated sites. During the challenge phase, very faint erythema (score 0.5) was noted for 12/20 test sites treated with the 1% w/w mixture at the 24 hour reading. Irritation persisted at 5/20 to 48 hours. Naive controls treated with the 1% w/w mixture exhibited very faint erythema at 2/10 treated sites at the 24 hour reading. Irritation cleared from these sites by 48 hours. Very faint erythema was noted for 2/20 test sites treated with the 0.3% w/w mixture, with irritation clearing by 48 hours. In control animals, very faint erythema was noted for 2/10 treated sites, with irritation clearing by 48 hours.

Based on the results of this study, Paraquat (240 g/L) and PP796 (1.5 g/L) SL (A7813K) does not have to be labeled as a dermal sensitizer.

This study is classified as acceptable. It does satisfy the guideline requirement for a primary dermal sensitization study (OPPTS 870.2600; OECD 406) in the Guinea pig .

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. PROCEDURE

A. Induction - Once a week for 3 weeks, 0.4 mL of a 10% w/w mixture of the test substance in distilled water was applied to the dose site of each animal using a lint patch and secured with surgical tape to 20 test animals. After 6 hours of exposure, the patches were removed. 24 and 48 hours after each induction the animals were scored for dermal irritation.

B. Challenge - Thirteen days after the last induction dose challenge doses of 0.2 mL of a 1% w/w mixture of the test substance in distilled water and a 0.3% w/w mixture were applied to the right side of the test animals for 6 hours. Approximately 24 and 48 hours after challenge, the animals were graded for dermal irritation.

C. Naive Controls - A naive control group of 10 animals were tested with 0.2 mL of the 1% w/w and 0.3% w/w mixture at challenge only.

II. RESULTS and DISCUSSION:

A. Reactions and duration - All animals survived and appeared healthy throughout the study. During the induction phase of the study, very faint to faint erythema (score 0.5-1) was noted for most of the treated sites. During the challenge phase, very faint erythema (score 0.5) was noted for 12/20 test sites treated with the 1% w/w mixture at the 24 hour reading. Irritation persisted at 5/20 to 48 hours. Naive controls treated with the 1% w/w mixture exhibited very faint erythema at 2/10 treated sites at the 24 hour reading. Irritation cleared from these sites by 48 hours. Very faint erythema was noted for 2/20 test sites treated with the 0.3% w/w mixture, with irritation clearing by 48 hours. In control animals, very faint erythema was noted for 2/10 treated sites, with irritation clearing by 48 hours.

B. Positive control - Results were appropriate with a HCA study to validate test procedures. The positive control study was completed July 2, 2004. This test was completed July 23, 2004.

C. Reviewer's Conclusions: Agree with study author.

Reviewer: Breann Hanson **Date:** Nov. 29, 2004
Risk Manager (EPA): Hope Johnson, RM 25

STUDY TYPE: Acute Oral Toxicity - Wistar rat; OPPTS 870.1100; OECD 425

TEST MATERIAL: Paraquat 200 g/l SL Formulation (A3879BU) (Paraquat: 18.416%, Batch Reference: J6470/11/1; clear green liquid)

CITATION: Johnson, I. (2003) Paraquat 200 g/l SL Formulation (A3879BU): Acute Oral Toxicity Study in the Rat - Up and Down Procedure. Laboratory Study Identification: AR7304. Unpublished study prepared by Central Toxicology Laboratory. July 15, 2003. MRID 46364515.

SPONSOR: Syngenta Crop Protection, Inc., P.O. Box 18300, Greensboro, NC 27419

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 46364515), 7 female Wistar Alpk rats (Age: 8-12 weeks, Weight: 166-254 g; Source: Rodent Breeding Unit, Cheshire, UK) were given a single oral dose of Paraquat 200 g/l SL Formulation (A3879BU) (Paraquat: 18.416%, Batch Reference: J6470/11/1; clear green liquid) by oral gavage. The study was initiated at a dose of 175 mg/kg in one female, and due to survival of that animal an additional 6 females were dosed at either 175, 550 or 2,000 mg/kg following the up-and-down procedure. Individual animal body weights were recorded prior to test substance administration and again on days 8 and 15, or at death. Clinical checks for mortality and signs of toxicity were made immediately post-dosing and a further twice on initial study day and at least once daily for 15 days. All animals were necropsied on study day 15, or as soon as possible after death.

The 1 animal dosed at 175 mg/kg survived, gained weight and appeared healthy throughout the study. No gross internal findings were observed at necropsy.

1/3 animals dosed at 550 mg/kg were killed *in extremis* on study day 6. The surviving animals either gained weight or equalled their initial body weight by the end of the study. Slight toxicity was seen until study day 4 in one animal, while the other animal showed no signs of toxicity. No gross internal findings were observed at necropsy.

3/3 animals dosed at 2,000 mg/kg died during the study. One was found dead on study day 1, one was found dead on study day 2 and the remaining was killed *in extremis* on study day 2. At necropsy, findings included contents of the stomach and/or intestines stained blue, staining of the mouth and fluid stomach contents were noted.

Oral LD_{50} Females = 550 mg/kg (95% C.I. = 186.5 to 1640)

Based on the LD_{50} in female rats, Paraquat 200 g/l SL Formulation (A3879BU) is classified as

EPA Toxicity Category III.
This acute oral study is classified as acceptable. It does satisfy the guideline requirement for an acute oral study (OPPTS 870.1100; OECD 425) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Individual animals were dosed as follows:

Main Test

Dosing Sequence	Animal No.	Sex	Dose level (mg/kg)	Sort-Term Outcome	Long-Term Outcome
1	21	F	175	S	S
2	32		550	S	S
3	47		2000	D	D
4	563		550	S	S
5	34		2000	D	D
6	48		550	S	D
7	130		2000	D	D

S = survival D = death

AOT425statpgm (Version: 1.0) Test Results and Recommendations
Acute Oral Toxicity (OECD Test Guideline 425) Statistical Program

Date/Time: Wednesday, November 24, 2004, 12:33:46 PM
Data file name: work.dat
Last modified: 11/24/2004 12:33:46 PM

Test/Substance: paraquat (200 g/l)
Test type: Main Test
Limit dose (mg/kg): 2000
Assumed LD50 (mg/kg): Default
Assumed sigma (mg/kg): 0.5

Recommended dose progression: 2000, 550, 175, 55, 17.5, 5.5, 1.75

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DATA:

Test Seq.	Animal ID	Dose (mg/kg)	Short-term Result	Long-term Result
1	21	175	O	O
2	32	550	O	O
3	47	2000	X	X
4	563	550	O	O
5	34	2000	X	X
6	48	550	O	X
7	130	2000	X	X

(X = Died, O = Survived)
Dose Recommendation: The main test is complete.
Stopping criteria met: 5 reversals in 6 tests.

SUMMARY OF LONG-TERM RESULTS:

Dose	O	X	Total
175	1	0	1
550	2	1	3
2000	0	3	3
All Doses	3	4	7

Statistical Estimate based on long term outcomes:

Estimated LD50 = 550 (The one dose with partial response).
95% PL Confidence interval is 186.5 to 1640.

A. <u>Mortality</u> - As noted in table.

B. <u>Clinical observations</u> - The 1 animal dosed at 175 mg/kg survived, gained weight and appeared healthy throughout the study.

1/3 animals dosed at 550 mg/kg were killed *in extremis* on study day 6. The surviving animals either gained weight or equalled their initial body weight by the end of the study. Slight toxicity was seen until study day 4 in one animal, while the other animal showed no signs of toxicity.

3/3 animals dosed at 2,000 mg/kg died during the study. One was found dead on study day 1,

one was found dead on study day 2 and the remaining was killed *in extremis* on study day 2.

C. Gross Necropsy - No gross internal findings were observed at necropsy for the animals dosed at 175 or 550 mg/kg.

At necropsy, findings for animals dosed at 2,000 mg/kg included contents of the stomach and/or intestines stained blue, staining of the mouth and fluid stomach contents were noted.

D. Reviewer's Conclusions: Agree with study author.

Reviewer: Breann Hanson **Date:** Nov. 29, 2004
Risk Manager (EPA): Hope Johnson, RM 25

STUDY TYPE: Acute Dermal Toxicity - Wistar Rat; OPPTS 870.1200; OECD 402

TEST MATERIAL: Paraquat 200 g/l SL Formulation (A3879BU) (Paraquat: 18.416%, Batch Reference: J6470/11/1; clear green liquid)

CITATION: Johnson, I. (2003) Paraquat 200 g/l SL Formulation (A3879BU): Acute Dermal Toxicity Study in the Rat. Laboratory Study Identification: CR3618. Unpublished study prepared by Central Toxicology Laboratory. July 16, 2003. MRID 46364514.

SPONSOR: Syngenta Crop Protection, Inc., P.O. Box 18300, Greensboro, NC 27419

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 46364514), 15/sex of Wistar Aplk rats (Age: 8-12 weeks; Weight: 245-322 g males, 176-277 g females; Source: Rodent Breeding Unit, Cheshire, UK) were dermally exposed to a single application of Paraquat 200 g/l SL Formulation (A3879BU) (Paraquat: 18.416%, Batch Reference: J6470/11/1; clear green liquid) at either 500, 1,000 or 2,000 mg/kg. The test material was applied to the shorn back of each animal for 24 hours using an occlusive dressing. Individual animal body weights were recorded prior to test substance administration and again on days 8 and 15, or after death. Clinical checks for mortality and signs of toxicity were made twice post-application on initial study day and at least once daily for 15 days. Animals were also graded for dermal irritation (Draize) after removal of the dressings and once daily for 14 days. All animals were necropsied on study day 15, or as soon as possible after death.

1/5 male dosed at 500 mg/kg was killed *in extremis* on study day 4. The remaining 4/5 males and 5/5 females survived the study. One female failed to gained body weight. There were no signs of toxicity in the surviving animals. Scabs and wet sores were apparent on some animals while moderate skin irritation, persisting to study termination, was noted in all animals. At necropsy, the male killed *in extremis* was noted as having stained fur and nares. Animals that survived to study termination were noted as having scabs and, in addition, females had thickened scaly skin.

3/5 males dosed at 1,000 mg/kg were found dead on study days 3 or 4 while 1/5 females were killed *in extremis*. All remaining animals survived the study and gained weight. There were no signs of toxicity in the surviving animals. Slight to moderate skin irritation, scabs and wet sores were apparent on animals. At necropsy, the males killed *in extremis* had no gross internal findings while the female had discoloured liver, lungs and nares, scabs and froth in the lumen. Animals that survived to study termination were noted as having scabs and, in addition, males had thickened skin.

All animals dosed at 2,000 mg/kg were found dead or killed *in extremis* on study day 2 or 3. Slight or moderate skin irritation was noted in most animals. At necropsy staining of the fur was noted on all animals and several animals had distended stomachs while two had staining of the mouth or nares.

Dermal LD_{50} Males => 805 mg/kg (95% C.I = 423-1264 mg/kg)
Females => 1,231 mg/kg (95% C.I. = 928-1632 mg/kg)

Based on the dermal LD_{50} of 805 mg/kg and 1,231 mg/kg, Paraquat 200 g/l SL Formulation (A3879BU) is classified as EPA Toxicity Category II.

This acute dermal study is classified acceptable. It does satisfy the guideline requirement for an acute dermal study (OPPTS 870.1200; OECD 402) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Dose (mg/kg)	Mortality/Number Tested		
	Males	Females	Combined
500	1/5	0/5	1/10
1000	3/5	1/5	4/10
2000	5/5	5/5	10/10

A. Mortality - As noted in table.

B. Clinical observations - 1/5 male dosed at 500 mg/kg was killed *in extremis* on study day 4. The remaining 4/5 males and 5/5 females survived the study. One female failed to gained body weight. There were no signs of toxicity in the surviving animals. Scabs and wet sores were apparent on some animals while moderate skin irritation, persisting to study termination, was noted in all animals.

3/5 males dosed at 1,000 mg/kg were found dead on study days 3 or 4 while 1/5 females were killed *in extremis*. All remaining animals survived the study and gained weight. There were no signs of toxicity in the surviving animals. Slight to moderate skin irritation, scabs and wet sores were apparent on animals.

All animals dosed at 2,000 mg/kg were found dead or killed *in extremis* on study day 2 or 3.

Slight or moderate skin irritation was noted in most animals.

C. Gross Necropsy - In animals dosed at 500 mg/kg, at necropsy the male killed *in extremis* was noted as having stained fur and nares. Animals that survived to study termination were noted as having scabs and, in addition, females had thickened scaly skin.

In animals dosed at 1000 mg/kg, at necropsy the males killed *in extremis* had no gross internal findings while the female had discoloured liver, lungs and nares, scabs and froth in the lumen. Animals that survived to study termination were noted as having scabs and, in addition, males had thickened skin.

In animals dosed at 2000 mg/kg, at necropsy staining of the fur was noted on all animals and several animals had distended stomachs while two had staining of the mouth or nares.

D. Reviewer's Conclusions: Agree with study author.

Reviewer: Breann Hanson **Date:** Nov. 29, 2004
Risk Manager (EPA): Hope Johnson, RM 25

STUDY TYPE: Primary Eye Irritation - NZW Rabbit, OPPTS 870.2400; OECD 405

TEST MATERIAL: Paraquat 200 g/l SL Formulation (A3879BU) (Paraquat: 18.416%, Batch Reference: J6470/11/1; clear green liquid)

CITATION: Johnson, I. (2003) Paraquat 200 g/l SL Formulation (A3879BU): Eye Irritation Study in the Rabbit. Laboratory Study Identification: FB6020. Unpublished study prepared by Central Toxicology Laboratory. August 1, 2003. MRID 46364512.

SPONSOR: Syngenta Crop Protection, Inc., P.O. Box 18300, Greensboro, NC 27419

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 46364512), 0.1 mL of undiluted Paraquat 200 g/l SL Formulation (A3879BU) (Paraquat: 18.416%, Batch Reference: J6470/11/1; clear green liquid) was instilled into the conjunctival sac of the left eye of 3 female young adult New Zealand albino rabbits (Source: Charles River UK Ltd., Kent, UK and Harlan Interfauna UK Ltd., Oxfordshire, UK). The untreated right eye served as a control. At first only one animal was treated and an assessment of the initial pain reaction was made. Animals were then observed at 1, 24, 48, 72 hours and on days 4, 7, 10, 14 and 17 days post-instillation. Irritation was scored according to Draize.

1 hour after instillation 3/3 eyes exhibited slight corneal opacity (score 1), iritis (score 1), conjunctivitis redness, chemosis and discharge (scores 1-2). All signs of irritation were resolved by study day 17, apart from slight discharge in 2 animals. Positive effects cleared within 10 days. Additional signs noted included comprised lachrymatory, Harderian or mucoid discharge, erythema, oedema, thickening and convolution of the eyelids, haemorrhage of the conjunctiva and nictitating membrane, dried secretion around the periorbital skin, irregular corneal surface and hair loss around the periorbital area. Two animals also exhibited salivation and few faeces.

The test substance is moderately irritating. In this study, Paraquat 200 g/l SL Formulation (A3879BU) is classified as EPA Toxicity Category II.

This study is classified as acceptable. It does satisfy the guideline requirement for a primary eye irritation study (OPPTS 870.2400; OECD 405) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS AND DISCUSSION:

	Number "positive"/number tested								
	Hours				Days				
Observations	1	24	48	72	4	7	10	14	17
Corneal Opacity	3/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
Iritis	3/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
Conjunctivae									
Redness*	2/3	3/3	3/3	3/3	3/3	2/3	0/3	0/3	0/3
Chemosis*	2/3	3/3	1/3	0/3	0/3	0/3	0/3	0/3	0/3
Discharge*	3/3	0/3	1/3	1/3	1/3	0/3	2/3	2/3	0/3

*Score of 2 or more required to be considered "positive"

A. Observations - 1 hour after instillation 3/3 eyes exhibited slight corneal opacity (score 1), iritis (score 1), conjunctivitis redness, chemosis and discharge (scores 1-2). All signs of irritation were resolved by study day 17, apart from slight discharge in 2 animals. Positive effects cleared within 10 days. Additional signs noted included comprised lachrymatory, Harderian or mucoid discharge, erythema, oedema, thickening and convolution of the eyelids, haemorrhage of the conjunctiva and nictitating membrane, dried secretion around the periorbital skin, irregular corneal surface and hair loss around the periorbital area. Two animals also exhibited salivation and few faeces.

B. Reviewer's Conclusions: Agree with the study author.

Reviewer: Breann Hanson **Date:** Nov. 29, 2004
Risk Manager (EPA): Hope Johnson, RM 25

STUDY TYPE: Primary Dermal Irritation - NZW Rabbit; OPPTS 870.2500; OECD 404

TEST MATERIAL: Paraquat 200 g/l SL Formulation (A3879BU) (Paraquat: 18.416%, Batch Reference: J6470/11/1; clear green liquid)

CITATION: Johnson, I. (2003) Paraquat 200 g/l SL Formulation (A3879BU): Skin Irritation Study in the Rabbit. Laboratory Study Identification: EB5012. Unpublished study prepared by Central Toxicology Laboratory. May 22, 2003. MRID 46364513.

SPONSOR: Syngenta Crop Protection, Inc., P.O. Box 18300, Greensboro, NC 27419

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 46364513), 3 female young adult New Zealand albino rabbits (Source: Charles River UK Ltd., Kent, UK) were dermally exposed to 0.5 mL of undiluted Paraquat 200 g/l SL Formulation (A3879BU) (Paraquat: 18.416%, Batch Reference: J6470/11/1; clear green liquid). Initially only one animal was treated and after consideration of the skin reactions in this animal two additional animals were treated. The test substance was applied to the left flank of each animal, covered with a gauze patch and secured with a strip of surgical tape for 4 hours. Animals were then observed for up to 34 days to assess the reversibility of skin reactions.. Dermal irritation was scored according to the Draize system at 1, 24, 48, 72 hours post-patch removal for all animals and in intervals for up to 34 days.

One hour post-patch removal very slight erythema (score 1) was noted at 2/3 treated sites. Irritation increased thereafter. At 72 hours very slight to moderate erythema (score 1-2) was noted in all animals, as well as very slight to slight oedema (score 1-2) for 2/3 animals. Erythema and oedema was seen in all animals up through 11 days, but not after. Additional signs of irritation noted included desquamation, scabbing, wrinkling, thickening and areas of new skin. Animals recovered from all signs of dermal irritation by study day 34.

In this study, the formulation is slightly irritating to the skin. Paraquat 200 g/l SL Formulation (A3879BU) is classified as EPA Toxicity Category IV.

This study is classified as acceptable. It does satisfy the guideline requirement for a primary dermal irritation study (OPPTS 870.2500; OECD 404) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

INDIVIDUAL SKIN IRRITATION SCORES

ERYTHEMA/EDEMA

Animal Number	Sex	Hours				Days			
		1	24	48	72	4	7	8	11
62	F	0/0	1/0	1/0	1/0	1/1	NA*	2/1	2/1
72		1/0	1/1	2/1	2/1	2/1	2/0	NA*	0/0
73		1/0	1/1	2/2	2/2	2/2	2/0	NA*	0/0
Severity of Irritation - Mean Score		0.66/ 0.0	1.0/ 0.66	1.66/ 1.0	1.66/ 1.0	1.66/ 1.33	2/ 0	2/ 1	0.66/ 0.33

*NA - animal was not scored.

A. Observations - One hour post-patch removal very slight erythema (score 1) was noted at 2/3 treated sites. Irritation increased thereafter. At 72 hours very slight to moderate erythema (score 1-2) was noted in all animals, as well as very slight to slight oedema (score 1-2) for 2/3 animals. Erythema and oedema was seen in all animals up through 11 days, but not after. Additional signs of irritation noted included desquamation, scabbing, wrinkling, thickening and areas of new skin. Animals recovered from all signs of dermal irritation by study day 34.

B. Results - Test substance is slightly irritating to the skin.

C. Reviewer's Conclusions - Agree with study author.

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Reviewer: Breann Hanson **Date:** Nov. 29, 2004
Risk Manager (EPA): Hope Johnson, RM 25

STUDY TYPE: Dermal Sensitization - Guinea Pig; OPPTS 870.2600; OECD 406

TEST MATERIAL: Paraquat 200 g/l SL Formulation (A3879BU) (Paraquat: 18.416%, Batch Reference: J6470/11/1; clear green liquid)

CITATION: Johnson, I. (2003) Paraquat 200 g/l SL Formulation (A3879BU): Skin Sensitization Study in the Guinea Pig. Laboratory Study Identification: GG7729. Unpublished study prepared by Central Toxicology Laboratory. August 26, 2003. MRID 46364516.

SPONSOR: Syngenta Crop Protection, Inc., P.O. Box 18300, Greensboro, NC 27419

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 46364516) with Paraquat 200 g/l SL Formulation (A3879BU) (Paraquat: 18.416%, Batch Reference: J6470/11/1; clear green liquid), 30 female young adult Hartley guinea pigs (Weight: 300-344 g males; Source: Harlan Interfauna UK Ltd., Oxon, UK) were tested using the Buehler method. Three times a week for 3 weeks, 0.4 mL of a 25% w/v mixture of the test substance in distilled water (for the first 3 inductions) or a 10%w/v mixture (for the final 6 inductions) was applied to the dose site of each animal using a lint patch and covered with an occlusive dressing to 20 test animals. During this phase 10 naive control guinea pigs were treated in the same manner but with deionized water only. After 6 hours of exposure, the patches were removed. 24 hours after each induction the animals were scored for dermal irritation. Two weeks after the last induction dose challenge doses of 0.1-0.2 mL of a 10% w/v mixture of the test substance in distilled water and a 5% w/v mixture were applied to either flank of the test animals and to the naive control guinea pigs for 6 hours. Approximately 24 and 48 hours after challenge, the animals were graded for dermal irritation. The procedures were validated using alpha-Hexylcinnamaldehyde (HCA) as the positive control substance.

Irritation was noted for all test animals during the induction phase while there were no signs of irritation in any of the control animals. There were no signs of irritation in any animal at challenge. One test animal was humanely killed prior to the 7th induction due to severe signs of toxicity.

Based on the results of this study, Paraquat 200 g/l SL Formulation (A3879BU) does not have to be labeled as a dermal sensitizer.

This study is classified as acceptable. It does satisfy the guideline requirement for a primary dermal sensitization study (OPPTS 870.2600; OECD 406) in the Guinea pig .

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality

statements were provided.

I. PROCEDURE

A. Induction - Three times a week for 3 weeks, 0.4 mL of a 25% w/v mixture of the test substance in distilled water (for the first 3 inductions) or a 10%w/v mixture (for the final 6 inductions) was applied to the dose site of each animal using a lint patch and covered with an occlusive dressing to 20 test animals. During this phase 10 naive control guinea pigs were treated in the same manner but with deionized water only. After 6 hours of exposure, the patches were removed. 24 hours after each induction the animals were scored for dermal irritation.

B. Challenge - Two weeks after the last induction dose challenge doses of 0.1-0.2 mL of a 10% w/v mixture of the test substance in distilled water and a 5% w/v mixture were applied to either flank of the test animals and to the naive control guinea pigs for 6 hours. Approximately 24 and 48 hours after challenge, the animals were graded for dermal irritation.

C. Naive Controls - A naive control group of 10 animals were tested with the test substance at challenge only.

II. RESULTS and DISCUSSION:

A. Reactions and duration - Irritation was noted for all test animals during the induction phase while there were no signs of irritation in any of the control animals. There were no signs of irritation in any animal at challenge. One test animal was humanely killed prior to the 7^{th} induction due to severe signs of toxicity.

B. Positive control - Results were appropriate with a HCA study to validate test procedures. The positive control study was completed May 31, 2003 This test was completed May 2, 2003.

C. Reviewer's Conclusions: Agree with study author.

1. **DP BARCODE:** D309349
2. **PC CODE:** 061601
3. **CURRENT DATE:** 29/NOV/2004
4. **TEST MATERIAL:**

[a] Paraquat 240 g/l SL Formulation (A7813K) (Paraquat: 22.3%, Batch Reference: J4267/75-2; green liquid)
[b] Paraquat (240 g/L) and PP796 (1.5 g/L) SL (A7813K) (Paraquat: 22.3% w/w, Batch Reference: J4267/75-2; clear green liquid)
[c] Paraquat 200 g/l SL Formulation (A3879BU) (Paraquat: 18.416%, Batch Reference: J6470/11/1; clear green liquid)

Study/Species/Lab Study # /Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity/rat [a] SafePharm Laboratories Ltd. 006-438/08-03-2004	46364503	LD_{50} = 310 mg/kg (95% C.I.= 175-550 mg/kg) (females)	II	A
Acute dermal toxicity/rat [a] SafePharm Laboratories Ltd. 006-439/08-03-2004	46364505	LD_{50} > 2,000 mg/kg (males, females combined)	III	A
Primary eye irritation/rabbit [a] SafePharm Laboratories Ltd. 006-407/07-14-2004	46364506	no corneal opacity or iritis noted. 3/3 conjunctivitis at 1 hour, no positive effects on day 28	II	A
Primary dermal irritation/rabbit [a] SafePharm Laboratories Ltd. 006-406/07-13-2004	46364504	moderate irritant	III	A
Dermal sensitization/guinea pig [b] Product Safety Laboratories 15409/07-23-2004	46364507	is not a sensitizer	–	A

Core Grade Key: **A =Acceptable, S = Supplementary, U = Unacceptable, W = Waived**

Study/Species/Lab Study # /Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity/rat [c] Central Toxicology Laboratory AR7304/07-15-2003	46364515	LD_{50} = 550 mg/kg (95% C.I.= 186.5 - 1640 mg/kg) (females)	III	A
Acute dermal toxicity/rat [c] Central Toxicology Laboratory CR3618/07-16-2003	46364514	LD_{50} = 805 mg/kg (males) LD_{50} = 1231 mg/kg (females)	II	A
Primary eye irritation/rabbit [c] Central Toxicology Laboratory FB6020/08-01-2003	46364512	3/3, opacity, iritis, conjunctivitis at 1 hour, no positive effects on day 10.	II	A
Primary dermal irritation/rabbit [c] Central Toxicology Laboratory FB5012/05-22-2003	46364513	slight irritant	IV	A
Dermal sensitization/guinea pig [c] Central Toxicology Laboratory GG7729/08-26-2003	46364516	is not a sensitizer	–	A

Core Grade Key: **A =Acceptable, S = Supplementary, U = Unacceptable, W = Waived**