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

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AUG 8 1984

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Brea Agricultural Service, Inc., EUP Request and Temporary Exemption from Tolerance

To: Mr. Robert Taylor, PM 25
Fungicide-Herbicide Branch
Registration Division (TS-767)

FROM: Michael J. Galvin, Ph. D.
Toxicology Branch
HED (TS-769)
18 July 1984 7/19/84

THROUGH: William Butler, Head
Review Section III
7-27-84

William Burnam, Chief
Toxicology Branch
8/18/84

Compound: Sy-83

Registration # 9018-EUP-R; 4G3039

Accession # 072330

Tox Chem # 517R

Registrant: Brea Agricultural Service, Inc.
Drawer I, Stockton, CA 95201

Action Requested:
The registrant requests an experimental use permit for a plant growth regulator,SY-83, on grapes, citrus, tomatoes, alfalfa, almonds, cherries, prunes, apples, peaches, nectarines, beans, corn, onions, peppers, potatoes, strawberries, sugarbeets, cucumbers, squash, melons, barley and wheat, without crop destruction; and temporary exemption from the requirements of a tolerance.

Recommendation
Toxicology branch recommends that the experimental use permit and a temporary exemption from tolerance be granted.

Compound
Sy-83 is identified as; L(+) lactic acid.
Physical state: Colorless and odorless liquid.

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Boiling point: 107°C, not flammable.
Solubility: Soluble in water.
Specific gravity: 1.2
Formulation (Confidential) : 80% L(+)lactic acid [redacted]

INERT INGREDIENT INFORMATION IS NOT INCLUDED

Toxicology Data Submitted

Reports of acute oral, acute dermal and dermal irritation studies have been submitted on SY-83. DERs on these studies are attached. The toxicity of the compound is summarized as follows:

Acute oral rats	Core classification: minimum LD_{50} = 4,936 mg/kg, males 3,543 mg/kg, females Tox. category III
Acute dermal rabbits	Core classification: minimum LD_{50} >2000mg/kg males & females Tox. category I, danger Severe dermal irritant No systemic toxicity
Dermal irritation rabbits	Core classification: minimum Tox. category I, danger Severe dermal irritant

Discussion

The toxicology data submitted on SY-83 is sufficient to support an experimental use permit. If Residue Chemistry Branch agrees that the amounts proposed do not exceed the amount for the exemption for tolerance when lactic acid is used as a solvent; Temporary Exemption can be granted. An eye irritation study was not required because the pH of the compound is less than 2 and would be expected to have corrosive properties (Tox category I). The severe dermal irritation properties of this product requires that skin and eye protection be worn during use. Lactic acid is naturally occurring in soils, as a bacterial fermentation product, and in humans and other animals after vigorous activity; but usually as a racemic mixture (± Lactic acid). However, because of the very low levels of L(+) lactic acid to be expected on the crops, this does not present a concern as to toxicity.

It should be noted that the registrant is requesting an unusually large acreage for chemical testing. Although the registrant states that this is necessary in order to provide reliable data, the acreage is primarily in regions where there is a profitable market. In addition, the registrant is planning to sell the treated crops to pay for the study. Therefore it appears that marketing rather than scientific concerns necessitate the large acreage. Since the chemical is on the GRAS list and already has an exemption from tolerance when used in pesticide formulations, the requested acreage can be approved. However the PM should remind the registrant that this is an unusual circumstance.

Data Evaluation Report
L(+) lactic acid (SY-83)
Acute Oral LD_{50}: Rats

Compound L(+) lactic acid, Tox. chem # 517R

Compound Numbers None

Citation Acute Oral LD_{50} Study in Rats Using SY-83. Wingard, B., Barnes,T.B., and MacKellar,D.G., Toxigenics Study 410-1369. January 6, 1984.

Report Number None

Reviewed By Michael J. Galvin, Ph.D. Michael J Galvin
19 July 1984

Core Classification Minimum

Tox Catagory III.

Conclusion L(+) lactic acid has an oral LD_{50} of 4,936 (4,453 - 5470) mg/kg for males and 3,543 (3,230 - 3,886) mg/kg for females. All mortalies occurred after dosing on day 0 or in the morning of day 1. Necropsy of found dead animals revealed abnormalities of the lung, stomach, liver, kidney and exudate in the nasal and/or oral regions. No other abnormalities were noted.

Materials
1. L(+)lactic acid (SY-83, Brea Agricultural Service,Inc.).
2. Young adult, albino rats, males and females, weighing between 189 and 256 grams (mean = 223 grams, males; 220 grams, females). From Charles River Breeding Laboratories, Inc., (Portage, MI facility), 251 Ballardvale Street, Wilmington, MA 01887.

Methods
1. Animals: Twenty males and 35 females were randomly assigned to the study at dose levels listed in section 1 of the results.
2. Duration of study: 14 days.
3. Dose/duration: One logarithmically spaced dose of SY-83 between 3,162 and 6,310 mg/kg per animal.
4. Application: Weight/weight suspensions of the test article in deionized water were administered by oral gavage in a single dose.
5. Observations during study:
   a. Animals were observed for mortality and abnormal clinical signs once each hour after dosing on day 0 (to the 4 to 5 hour interval), and twice daily thereafter for the duration of the study.
   b. Body weights were recorded prior to test article administration, and on days 7 and 14 for surviving animals and at the time found dead for other animals.
   c. All external surfaces, orifices, and organs; cranial cavity; carcass; external and cut surfaces of the brain; abdominal, thoracic, and pelvic

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cavities and their viscera; and cervical tissues and organs of each animal (found dead or killed on day 14) were examined at necropsy and all abnormal findings were recorded.

6. Termination of study: All surviving animals were rendered unconscious with carbon dioxide and exsanguinated.

7. Statistics: The oral LD_{50} value, the 95 percent confidence interval, and the slope of the dose-response curve, were calculated for each sex using a method adapted from Litchfield and Wilcoxon. Dose-response curves were prepared using the calculated LD_{50} data. The mean and standard error were calculated for body weight and test article administration data.

Results

1. The following is a summaty of mortalities observed during main study testing:

Dose level (mg/kg)	Number dead/number tested	
	Males	Females
3,162	---	1/5
3,548	---	2/5
3,981	---	5/5
4,467	1/5	5/5
5,012	3/5	5/5
5,623	4/5	5/5
6,310	5/5	5/5

--- = none tested

2. The oral LD_{50} values were determined to be 4,936 mg/kg for males and 3,543 mg/kg for females. The 95% confidence intervals were within 10.8% of the LD_{50} value for males and within 9.7% of the LD_{50} value for females.
3. Body weight gains were observed for all surviving animals on days 7 and 14 after dosing. Body weight loses were observed for all found dead animals.
4. Lethargy, ataxia, prostration, irregular breathing, piloerection, squinting, lacrimation, salivation, crusty muzzle, crusty eyes, loose stools, damp or yellow/brown stained fur in the perianal region, and moribund were abnormal clinical signs observed as early as 0 to 1 hour after dosing and as late as day 2.
5. Abnormalities were observed during necropsy of all animals that were found dead, and for the 4 surviving females dosed at 3,162 mg/kg. Abnormalites were observed in the lung, stomach (especially erosion), liver, kidney, and a red-brown exudate in the nasal and/or oral regions. No other abnormalities were noted during necropsy. No abnormalities were observed in the 3,548 dose females which survived till day 14.

Discussion:

This study is complete as to the Pesticide Assessment Guideline, Section 81-1, Acute Oral Toxicity. This is a scientifically sound study, and provides definitive information on the acute oral toxicity of L(+)lactic acid. The mechanism of the toxicity which occurs only at very high doses, is due to the severe splanchnic organ damage (stomach, liver and kidney) caused by the corrosive property of SY-83.

Data Evaluation Report
L(+) lactic acid (SY-83)
Primary Dermal Irritation: Rabbits

Compound L(+) lactic acid, Tox. chem # 517R

Compound Numbers None

Citation Primary Dermal Irritation Study in Rabbits Using SY-83. Wingard,B., Barnes,T.B., and MacKellar,D.G., Toxigenics, Inc.,1800 East Pershing Road, Decatur, IL 62526 ToxiGenics Study 410-1355. November 16, 1983.

Report Number None.

Reviewed By Michael J. Galvin, Ph.D. Michael J Galvin
30 May 1984

Core Classification Minimum

Tox Catagory I, Danger.

Conclusion L(+) lactic acid caused severe dermal irritation at all tested sites when 0.5 milliliters of the test article was applied neat for 24 hours to rabbits. Exposure caused no abnormal clinical signs.

Materials
1. L(+)lactic acid (SY- 83, Brea Agricultural Service,Inc.)
   Density = 1.195.7 milligrams/milliliter, pH = 1.83.
2. New Zealand White albino rabbits, males and females. Animal weight not provided. From Langshaw Farms, Route 1, Box 256, Augusta, MI 49012.

Methods
1. Experimental groups: one group consisting of 3 males and 3 females. Animals were assigned to the study by sequential number from a resident population which had been assigned random numbers.
2. Duration of study: 25 hours
3. Dose/duration: one-half(0.5)milliliter applied neat to each of the 4 test sites on the dorsal surface of each animal/24 hours.
4. Application: Sites were prepared by clipping the hair 24 hours prior to application of the test material. Two sites on each rabbit were abraded with a needle to penetrate the stratum corneum. The material was applied with a gauze patch, and the entire trunk was wrapped with an impervious binder.

Results

1. All animals survived the 25 hour duration of the study, and no abnormal clinical signs were observed,
2. Moderate to severe erythema and edema was observed for all but two sites. The individual data are presented in Table 1 (taken from Table 2 of Toxigenics study No. 410-1355).
3. Because of the severity of the reactions the study was terminated 60 minutes after removal of the test material.

Discussion

This report is complete as to the Pesticide Assessment Guideline, Section 81-5, Primary Dermal Irritation Study. This is a scientifically sound study, and provides definitive information on the irritant property of L(+) lactic acid. The mechanism of the effect appears to be due to the low ph of the product. Skin and eye protection will be necessary during use.

Table 1
Primary Dermal Irritation Study in Rabbits[a]

Rabbit Number	Intact Sites				Abraded Sites			
	Right side		Left side		Right Side		Left side	
	Erythema	Edema	Erythema	Edema	Erythema	Edema	Erythema	Edema
BB5166	4[b]	4	3[b]	4	4[by]	4	4[by]	4
BB5168	3[bys]	2	3[b]	4	3[b]	2	3[b]	4
BB5170	3	4	3	4	4[by]	4	4[by]	4
BB5194	4[bys]	4	4[by]	4	4[bys]	4	4[bys]	4
BB5195	4[by]	4	4[by]	4	4[bys]	4	4[by]	4
BB5196	4[bys]	4	4[bysr]	4	4[bys]	4	4[bys]	4

a. Evaluation was done 30 to 60 minutes after test article removal.
b. Blanching
s. Skin missing at part of test site.
y. Yellow-brown color of skin at part of test site.
r. Red exudate from test site.

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Data Evaluation Report
L(+) lactic acid (SY-83)
Acute Dermal Toxicity: Rabbits

Compound L(+) lactic acid, Tox. chem # 517R

Compound Numbers None

Citation Acute Dermal Toxicity Study in Rabbits Using SY-83 at a Dose Level of 2 Grams Per Kilogram of Body Weight. Wingard,B., Barnes,T.B., and MacKellar,D.G., ToxiGenics Study 410-1354. November 16, 1983.

Report Number None.

Reviewed By Michael J. Galvin, Ph.D. Michael J. Galvin
29 May 1984

Core Classification Minimum

Tox Catagory IV

Conclusion L(+) lactic acid causes severe dermal irritation, but no systemic toxicity at a dose of 2 grams/kilogram body weight. Necropsy revealed that abnormalities were characterized by brown, crusted and raised discolorations of the treated areas which also exhibited initial stages of recovery. However, because of the severe nature of the dermal irritation, this product would be expected to cause scarring. A dermal LD_{50} is not required because no lethality was observed at the tested dose.

Materials
1. L(+)lactic acid (SY- 83, Brea Agricultural Service,Inc.)
   Density = 1.195.7 milligrams/milliliter.
2. New Zealand White albino rabbits, males and females, weighing between 2.6 and 3.5 kilograms (mean = 2.95(males) and 3.02(females). From Langshaw Farms, Route 1, Box 256, Augusta, MI 49012.

Methods
1. Five males and 5 females were assigned to the study by sequential number from a resident population which had been assigned random numbers.
2. Duration of study: 14 days
3. Dose/duration: 2 grams/kilogram for 24 hours.
4. Application: The dorsal trunk (10% body surface) was clipped of hair 24 hours prior to test material application. The site was abraded with a needle to penetrate the stratum corneum. The test material was introduced under an impervious binder which was around the trunk and spread over the site.

5. Observations during study:
   a. Animals were observed for mortality and abnormal clinical signs hourly after dosing on day 0 (to the 2 to 3 hour interval) and twice daily thereafter for the duration of the study.
   b. The skin condition of the animal was evaluated each day of the observation period following test article removal. Dermal reaction scores were assigned using the Draize system.
   c. Body weights were recorded prior to test article application on day 0, on day 7, and prior to killing on day 14.

6. Termination of study: All animals were killed on day 14 by barbiturate injection followed by exsanguination. All external surfaces, orifices, and organs; cranial cavity; carcass; external and cut surfaces of trhe brain; abdominal, thoracic, and pelvic cavities and their viscera; and cervical tissues and organs of each animal were examined at necropsy. All abnormalities observed were recorded.

7. Statistics: The mean, standard deviation, and standard error were calculated for the body weight data, and for the test article application data.

Results

1. All animals survived the 14 day duration of the study. No abnormal clinical signs were observed during the study. All animals gained body weight.
2. Dermal reactions are summarized in Table 1.
3. Necropsy data are summarized in Table 2.

Discussion

This report is complete as to the Pesticide Assessment Guideline, Section 81-2, Acute dermal toxicity. However there needs to be a minor clarification of the necropsy data. The methods and tabular results indicate 5 animals of each sex were necropsied, however the summary and results narative state there were 3 of each sex necropsied. Based on the data presented, the correct number of necropsied animals is 5. This is a scientifically sound study, and provides definitive information on the irritant property of L(+) lactic acid. The mechanism of the effect appears to be due to the low pH of the product. Skin and eye protection will be necessary during use.

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Table 1
Summary of Dermal Reaction Data
Acute Dermal Toxicity Study in Rabbits

Sex	N[a]	Dermal Reaction	Average High Grade[b]	Average Low Grade[b]	Number Animals Present[c]	Days Noted
M	5	Erythema	4	3	5	1-14
		Edema	4	1.8	5	1-14
		Blanching	+	-	5	1-2.6
		Necrosis	+	-	5	1-3.6
		Eschar	+	-	5	2-13.5
		Atonia	+	-	5	4-11
		Desquamation	+	-	5	10.5-14
F	5	Erythema	4	3.4	5	1-14
		Edema	4	3	5	1-14
		Blanching	+	-	5	1-1.6
		Necrosis	+	-	5	1-11
		Eschar	+	-	3	2-13.6
		Atonia	+	-	5	4-14
		Desquamation	+	-	5	11-14

a. N= number of animals tested
b. Mean high or low score for reaction. If + reaction present, if - reaction not observed.
c. Number of rabbits in which the reaction was observed.

Table 2
Summary of Necropsy Data
Acute Dermal Toxicity Study in Rabbits

Sex	N[a]	Mean Day of Death	Number Dying Early[b]	Organ Affected	Abnormality[c]	Number Observed[d]
M	5	14	0	Skin	Discoloration(3) Depression(3) Crusted(3)	5
				Lung	Deep red focus	1
F	5	14	0	Skin	Discoloration(3) Crusted(3) Depression(3)	4

a. N= number of animals tested.
b. Number of animals dying before scheduled kill.
c. Abnormality (number of animals in which abnormality is noted)
d. Number of animals presenting with organ abnormality on day 14 after application of test material.

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