UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

00C047

DATE: March 9, 1979

SUBJECT: Tolerances Requested for Residues of Lasso [2-chloro-2',6'-diethyl-N-(methoxymethyl)acetanilide] in or on Sugarcane and Sugarcane Forage and Fodder.

FROM: Larry Anderson
Toxicology Branch, HED (TS-769)

TO: Robert Taylor
Product Manager#25

& Chemistry Branch

Petition No. 9F2144.

Petitioner: Monsanto Chemical Co.

Caswell [redacted]

Shaughnessy#09050

Registration#524-314

Tolerances Requested: 0.2 ppm in or on sugarcane and sugarcane forage and fodder.

Recommendations: It is recommended that the requested tolerances not be established at this time. Long-term and special studies (e.g., subacute and chronic feeding, reproduction, oncogenicity, teratology, and mutagenicity) submitted to support proposed tolerances for Lasso are based on data obtained from Industrial Bio-Test Laboratories, Inc. Validation reviews of the raw data supporting these IBT studies should be conducted by the registrant and provided to TOX to permit an acceptable decision regarding the usefulness of these studies towards satisfying regulatory requirements. In lieu of listing each individually, descriptions of the IBT studies which should be validated can be found in the following reviews:

1) The present review (3/?/78, Acc. Nos. 091278 and 234629) for PP#9F2144.

2) Review by L. Anderson (8/26/78, Acc. Nos. 234629 and 234630) of additional data submitted in support of EPA Reg. No. 524-314, -285, -296, and -304.

3) Review by W. Greear (1/20/78, Acc. Nos. 091278 and 091277) for PP#7G2002 and 524-EUP-39.

In the above 3 reviews, IBT studies are described which include those done with the Lasso technical material in support of tolerances and registration of the technical and those done to support registration and possible additional uses for various Lasso formulations.

*No RPAR criteria have been exceeded. However, epichlorohydrin, an ingredient in several Lasso formulations, is an RPAR candidate based on neurotoxicity in chickens and eye effects in humans.

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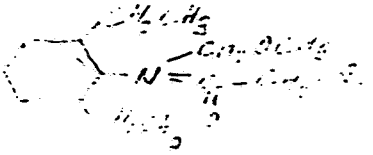
Permanent Tolerances: 3 ppm in or on peanut forage and hay; 1.5 ppm in or on peanut hulls; 0.75 ppm in or on soybean forage; 0.2 ppm in or on corn fodder and forage, corn grain, cotton forage, forage and hay of peas and beans, and soybeans; 0.1 ppm in or on field (dry) beans, green lima beans, peas with pods, and potatoes; 0.05 ppm in or on cottonseed, fresh corn including sweet corn (kernels plus cob with husk removed), and peanuts; 0.02 ppm in or on milk, eggs, meat, fat, and meat byproducts of cattle, goats, hogs, horses, poultry, and sheep (CFR 180.249).

Temporary Tolerances: 10 ppm in or on peanut forage and hay.

Chemical Name: 2-chloro-2',6'-diethyl-N-(methoxymethyl) acetanilide.

Synonyms: Alachlor, CP50144, Lasso

Chemical Structure:



Composition of Technical Product:

Components	Percent*
2-chloro-2',6'-diethyl-N-(methoxymethyl) acetanilide	90-94%
[redacted]	

*% of all components in the technical product was not reported.

**Impurities

[redacted]

Physical/Chemical Data:

a) Appearance: White, crystalline solid
b) Melting Point: 40-41 °C
c) Specific Gravity: 1.133 (25/15.6°C)
d) Solubility: Soluble in ether, acetone, benzene, alcohol, ethyl acetate; slightly soluble in hexane; insoluble in water.

Proposed Use: Herbicide

Application Rate: 3 Quarts/Acre ≈ 3Pounds Active Ingredient/Acre

Application Frequency: Once/season

Pre-harvest Treatment: Within 7 days prior to planting.

Post-harvest Treatment: None

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PRODUCT IMPURITY INFORMATION IS NOT INCLUDED

Background Toxicity Data:

References:

1) Review of G.E. Whitmore (11/27/67), PP#7F0622, establishing a PADI for man of 0.0025 mg/kg/day and approving tolerances of 0.2 ppm in or on corn grain, corn forage, and soybeans.

2) Review by W. Greear (1/20/78), PP#7G2002, approving a tolerance of 10 ppm in or on peanut forage and hay.

Studies:

1) Acute Toxicity

a) Oral and Dermal LD50 Determinations.

Formulation	Species	Oral LD50 (mg/kg)	Dermal LD50 (mg/kg)
Technical	Rat	1200	
Technical	Rabbit		>2000
10G	Rat	9300	
10G	Rabbit		>10,200
46.2% EC	Rat	3000	
46.2% EC	Rabbit		3500

b) Eye and Skin Irritation, Inhalation Toxicity.

Formulation	Species	Exposure	Observation
Technical	Rabbit	0.5 g on skin	0/8
Technical	Rabbit	10% soln. on skin	0.6/8
Technical	Rabbit	100 mg in eye, rinsing at 24 hrs.	17.6/110 at 1 hr., 0/110 at 120 hrs.
Technical	Rat	>24 mg/L, 1 hr.	No deaths
Technical	Rabbit	100 mg in eye	17/110 at 1 hr., corneal opacity gone at 3 days.

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Formulation	Species	Exposure	Observation
46.2% EC	Rat	>24.2 mg/L, 1 hr.	No deaths
46.2%	Rabbit	0.1 ml in eye, rinsing at 24 hrs.	Redness, slight edema
46.2%	Rabbit	0.1 ml in eye	46.3/110 max., edema and redness at 7 days.
TOG	Rabbit	100 mg in eye, rinsing at 1 min.	Irritation through 48 hrs., corneal opacity through 24 hours.
TOG	Rabbit	0.5 ml on skin	0/8

2) Subacute and Special Studies.

Formulation	Species	Type of Study	Observation
Technical	Rat	90-day feeding	NEL = 200 ppm
Technical	Dog	90-day feeding	NEL = 200 ppm
TOG	Rabbit	21-day dermal	NEL = 2g/kg/day
Lasso Metabolite	Dog	90-day feeding	NEL = 200 ppm
Lasso Metabolite	Rat	90-day feeding	NEL = 200 ppm

3) Chronic Studies

Chronic toxicity studies previously have not been submitted for review.

Review of Present Data

Studies described below have been submitted with PP#9F2144 and have not been previously reviewed.

A. Eye Irritation Study of CP50144 in Rabbits (Younger Laboratories, Inc., Project No. Y-68-118, 12/2/68, submitted by Monsanto Agricultural Products Co., 11/8/78, Acc. No. 092036).

1) Procedure

Into each right eye of albino male and female rabbits was placed 0.1 ml of test sample. Untreated left eyes were controls. The study was organized as follows:

Test Sample	# Rabbits/Group	Duration of Exposure*
Undiluted	3	11 days
"	3	2 seconds
"	3	4 seconds
Diluted (3 lb sample/20 gal. water)	3	24 hours
"	3	2 hours
"	3	30 minutes
Undiluted	3	24 hours
"	3	2 hours
"	3	30 minutes

*Eyes were rinsed with isotonic saline solution on termination of exposure.

Injuries were graded according to the method of Draize et al. (1944) at 1 hour and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 11 days post-treatment. Photographs of eyes exposed for the longest duration to diluted and undiluted test material were provided.

2) Results

	Draize Score (Numerical Average/110)			
Treatment Group	1 Hour	1 Day	3 Days	7 Days
Undiluted, unwashed	55.3	48.6	29.0	12.3
Undiluted, 2 sec.	30.6	33.6	11.6	2.0
Undiluted, 4 sec.	36.6	40.6	17.3	2.0
Diluted, 24 hours	15.3	9.3	4.3	0*
Diluted, 2 hours	13.6	7.3	2.6	0*
Diluted, 30 minutes	11.0	8.3	2.0	0*
Undiluted, 24 hours	55.3	45.6	26.3	13.3
Undiluted, 2 hours	51.6	43.3	27.0	12.0
Undiluted, 30 minutes	37.6	42.0	24.0	9.6

*5 Days

Discomfort, lacrimation, edema, and corneal dullness were observations common to all treatment groups during the first hour following treatment. Either opacity, dullness, or cloudiness of the cornea was found in all groups. Corneal opacity persisted through 7 days post-treatment in animals exposed to undiluted test material for 30 minutes or longer.

3) Conclusions

a) Classification: Supplementary Data

i) CP50144 is a synonym for the solid technical grade material. In the present study the 0.1 ml volume of test sample placed into the eye refers to both diluted and undiluted CP50144. It is not clear whether 0.1 ml refers to a volume equivalent of solid CP50144 or an undiluted liquid formulation designated CP50144, and clarification of this detail is requested. Otherwise, the use of several exposure groups and the persistence of corneal opacities through 7 days in animals exposed to undiluted test material for 30 minutes or longer adequately define the hazard to the eye.

b) Tox. Cat.: I (Provisional). Washing eyes exposed to undiluted test material within 30 minutes post-treatment was beneficial.

B) Acute Toxicity Studies on CP50144, 4 LBS/GAL E.C., in Rats and Rabbits (Industrial Bio-Test Laboratories, Inc., IBT No. A5487, 9/1/67, submitted by Monsanto Agricultural Products, Inc., 11/8/78, Acc.#091278).

B.1. Acute Oral LD50 Study in Rats.

1) Procedure

Sixteen Sprague-Dawley albino rats, 155-200g, were divided into 4 groups of 4 animals each (2 males and 2 females) which were administered 0.9, 1.4, 2.0 or 3.0 g/kg of undiluted test material by gavage. Observations for mortality, toxic signs, and body weight changes were continued during 14 days post-treatment. Necropsies were done.

2) Results

a) Mortality: LD50 = 1.8 $\pm$ 0.2 g/kg

b) Toxic Signs: Salivation, hemorrhagic rhinitis, hypoactivity, muscular weakness, intermittent tremors, hyperpnea.

c) Body Weight Changes: Unremarkable

d) Necropsy:

i) Survivors: Unremarkable

ii) Decedents: Pale, granular livers

3) Conclusions

a) Classification: Core-Minimum Data

i) Although only 2 animals/sex/dosage level were used, the acute oral toxicity of the test matieral is considered to be sufficiently defined.

ii) Body weights in conjunction with food intake were not recorded daily.

b) Tox. Cat.: III

B.2. Acute Dermal LD50 Study in Rabbits.

1) Procedure

Sixteen young adult New Zealand albino rabbits were divided into 4 groups of 4 animals each (2 males and 2 females) which received dermal applications of 3.0, 4.6, 6.8, or 10.2 g/kg of test material under occlusive dressing. Dressing and residual test material were removed at 24 hours after application. The animals were observed for mortality, toxic signs, and body weight changes during 14 days post-treatment. Necropsies were done.

2) Results

a) Mortality: LD50 = 5.0 $\pm$ 1.0 g/kg

b) Toxic Signs: Erythema, edema, and eschar formation at test sites.

c) Body Weight Changes: Dose-related loss or reduction of gain.

d) Necropsy: Unremarkable

3) Conclusions

a) Classification: Core-Minimum Data

i) At least 4 animals/sex/dosage level with half of the animals abraded should have been used. However, the present study is considered an acceptable evaluation of the relative dermal toxicity of the test material.

ii) Body weights in conjunction with food intake were not determined daily.

b) Tox. Cat.: III

B.3. Acute Vapor Inhalation Toxicity Study in Rats.

1) Procedure

Ten (5 males and 5 females) young adult Sprague-Dawley albino rats, 250g av. wt., were placed into a 70L inhalation chamber and were exposed for 1 hour to 32.6 mg/L of undiluted test material generated as a vapor. Observations for mortality, toxic signs, and body weight changes were made over 14 days post-exposure. Necropsies were done.

2) Results

a) Mortality: None LC50 > 32.6 mg/L, 1 hour

b) Toxic Signs: Salivation, clear nasal discharge, tremors, ataxia, anesthetization by the end of exposure with recovery within 10 minutes.

c) Body Weight Changes: Unremarkable

d) Necropsy: Unremarkable

3) Conclusions

a) Classification: Core-Minimum Data

i) The analytical concentration of vapor was not estimated.

ii) Body weights in conjunction with food intake were not determined daily.

b) Tox. Cat.: IV

B.4. Eye Irritation Study in Albino Rabbits.

1) Procedure

Into each right eye of 5 young adult New Zealand albino rabbits was instilled 0.1 ml of undiluted test material. Untreated left eyes were controls. Injuries were graded according to the method of Draize et al. (1944) at 1, 24, 48, 72, 96, and 168 hours post-treatment.

2) Results

Eye Injuries: Scores of 61.6, 59.6, and 63.0 at 1, 3, and 7 days, respectively. Corneal opacities found in all rabbits were not reversed within 7 days following treatment.

3) Conclusions

a) Classification: Core-Minimum Data

i) The possible benefit of washing eyes following treatment was not evaluated.

b) Tox. Cat.: I

B.5. Primary Skin Irritation Study in Albino Rabbits.

1) Procedure

Onto both abraded and intact test sites on each of 4 albino rabbits was applied 0.5 ml of undiluted test material under occlusive dressing. Dressing was removed at 24 hours following application. Irritation was scored according to the procedure of Draize et al. (1944) at 24 and 72 hours post-treatment.

2) Results

Skin Irritation: P.I. Index = 6.0

3) Conclusions

a) Classification: Core-Minimum Data

i) Only 4 animals were used, but the results are conclusive.

ii) Scoring for individual animals was not reported.

b) Tox. Cat.: II

C. Two-Year Chronic Oral Toxicity Study of Lasso Technical in Albino Rats. Ind. Bio-Test Laboratories, Inc., IBT#621-01180, 9/16/77, submitted by Monsanto Agricultural Products Co., 8/16/78, Acc. No. 234629).

1) Procedure

Four hundred eighty Charles River albino rats, 139-165g, were divided into 4 groups of 120 animals each (60 males and 60 females) which received 0, 100, 300, or 1000 ppm of test material in the diet for 2 years. Two hundred eighty rats (35/sex/dosage level) were housed individually, and 200 rats (25/sex/dosage level) were group-housed (3 rats/cage). Body weights were recorded weekly during the first 3 months and monthly thereafter. Food consumption was estimated weekly during the first 11 months and 1 week/month thereafter. Animals were observed for mortality and toxic signs daily. Blood and urine from 10/rats/sex in the control and 1000 ppm groups were analysed at 3, 6, 12, 18, and 24 months. Blood from 10/rats/sex in the 100 and 300 ppm groups and urine from 10 males in the 100 and 300 ppm groups were evaluated at 24 months. Hematologic, clinical chemistry, and urine analyses were based on the following parameters:

Hematology: Total leukocyte count, erythrocyte count, hemoglobin concentration, hematocrit value, differential leukocyte count.

Clinical Chemistry: Glucose, blood urea nitrogen, SAP, SGPT, protein, bilirubin, A/G ratio.

Urine Analysis: Glucose, albumin , pH, specific gravity, microscopic elements, bilirubin..

All survivors and all decedents not extensively autolysed were subjected to necropsy. Weights of brains, gonads, hearts, kidneys, livers, and spleenswere estimated. Histopathological examination of the following tissues and organs from all survivors in the control and 1000 ppm groups as well as animals found dead or killed while moribund was done:

Heart	Small and Large Intestines	Prostate
Lungs	Kidneys	Uterine horns
Trachea	Urinary bladder	Brain
Liver	Pituitary	Spinal cord
Spleen	Thyroid	Peripheral nerve
Lymph nodes	Parathyroid	Eye
Pancreas	Adrenals	Optic nerve
Stomach	Gonads	Salivary glands
Skeletal muscle	Bone marrow	

Additionally, neoplasms found during necropsy were examined microscopically.

2) Results

a) Mortality at 2 Years:

	Control		100 ppm		300 ppm		1000 ppm	
	M	F	M	F	M	F	M	F
No. Dead	33	32	26	32	38	34	36	42
No. Tested	60	60	60	60	60	60	60	60

b) Toxic Signs: Unremarkable

c) Body Weight Changes:

		Body Weight(g) at Week Indicated			
Dosage Group	Initial	13	52	78	104
Control, Male	166	484	615	669	633
Control, Female	145	280	367	424	462
100 ppm, Male	166	476	631	660	637
100 ppm, Female	147	286	375	431	487
300 ppm, Male	166	492	632	627	646
300 ppm, Female	139	282	365	390	394
1000 ppm, Male	165	469	603	621	616
1000 ppm, Female	147	276	361	413	436

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2) Results

Treatment was discontinued after 4 applications because of the severe skin reaction (erythema and edema at and extending beyond the test sites) elicited by concentrated test material. Testing with a 1/40 aqueous emulsion was not attempted since the preparation was heterogeneous.

3) Conclusions

a) Classification: Supplementary Data

i) The marked irritancy of the test material precluded an adequate evaluation of skin sensitization.

ii) The human subjects should have been more fully described to include, for example, sex, age, and race.

b) Skin sensitization potential of the test material cannot be determined.

E. Repeated Insult Patch Test with Lasso Technical Emulsifiable Concentrate in Humans (Industrial Biology Research and Testing Laboratories, Inc., No. M-7, 3/5/68, submitted by Monsanto Agricultural Products Co., 8/16/78, Acc. No. 234629).

1) Procedure

The method described in part D.1. of the present review was used. Aliquots of 0.1 ml of a 1/40 emulsion of test material/sq. cm. of skin were applied to 28 male and 28 female humans. Subjects received 8 applications of test substance.

2) Results

No reactions to the test material were found in 24 subjects. Extreme irritation, including erythema, edema, vesiculation, and ulceration, at and extending beyond the contact sites was observed in 19 subjects after the second application.

In 18 of 19 responsive subjects, new contact sites selected for subsequent applications showed delayed reactions of similar severity. During the post-treatment observation period, 5 additional subjects exhibited similar delayed reactions. Irritation was reduced in severity with medication.

3) Conclusions

a) Classification: Core-Guidelines Data

i) The results clearly define the irritation and sensitization potential of the test material on human skin.

b) The test material is a skin sensitizer.

3) Conclusions

Until the IBT studies discussed in Recommendations are validated, it is concluded that an adequate evaluation of the toxicity data submitted in support of the requested tolerances cannot be made at this time.

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Addendum

The following formulations of Lasso have been submitted*:

1. Lasso 4EC (EPA Reg. No. 524-314)

Ingredient	Percent
A) Active	
1) 2-chloro-2',6'-diethyl-N-(methoxymethyl) acetanilide	45.10
B) Inerts	[redacted]
	100.00%

INERT INGREDIENT INFORMATION IS NOT INCLUDED

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2) Lasso II (formally Granular Lasso 15) (EPA Reg. No. 524-296, 1/14/78).

Ingredients	% by Wt.
A) Active	
1) 2-chloro-2',6'-diethyl-N-(methoxymethyl) acetanilide	15.00
B) Inerts	[redacted]
	100.00

3) Lasso EC (EPA Reg. No. 524-285).

Ingredients	% by Wt.
A) Active	
1) 2-chloro-2',6'-diethyl-N-(methoxymethyl) acetanilide	42.97
B) Inerts	[redacted]
	100.00

INERT INGREDIENT INFORMATION IS NOT INCLUDED

TOX/HED:th:RD Initial WA:CO:FCW:3-9-79