12-9-91

MEMORANDUM:

Subject: EPA File Symbol/EPA Reg. No.: 7501-31 Lorsban 30 Flowable

From: Mark Perry, Biologist
Precautionary Review Section
Registration Support Branch
Registration Division (H7505C)

MP 11-25-91

To: Dennis Edwards, PM 19
Insecticide-Rodenticide Branch
Registration Division (H7505C)

Thru: Thomas C. Ellwanger, Section Head
Precautionary Review Section
Registration Support Branch
Registration Division (H7505C)

E 12/9/91

Applicant: Gustafson, Inc.
P.O. Box 660065
Dallas, TX 75266-0065

FORMULATION FROM LABEL:

	% by wt.
Active Ingredient(s): Chlorpyrifos (0,0-diethyl 0-(3,5,6-trichloro-2-pyridyl)phosphorothioate)	30.0
Inert Ingredient(s):	70.0
Total:	100%

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BACKGROUND

Gustafson Incorporated submitted acute oral, acute dermal, acute inhalation, primary eye irritation, primary dermal irritation, and dermal sensitization studies for review. Also, the registrant has proposed new precautionary labeling which includes a change in signal word from "warning" to "caution". The product is Lorsban 30 Flowable and the active ingredient is chlorpyrifos (0,0-diethyl 0-(3,5,6-trichloro-2-pyridyl) phosphorothioate) 30.0%. All studies were performed by Stillmeadow and the MRID numbers are 420013-01 through 420013-06.

RECOMMENDATION

The acute oral, acute inhalation, eye irritation, and dermal irritation studies are acceptable and have been graded core guideline. The acute dermal toxicity study is acceptable as core minimum data, and the dermal sensitization study is unacceptable and has been graded supplementary.

(1) The acute dermal toxicity study received a core minimum grade since it employed animals which were significantly above the weight limits specified in the Pesticide Assessment Guidelines.

(2) The dermal sensitization study is unacceptable for the following reasons:

a. Ethanol was employed as the vehicle for both induction and challenge. Since ethanol is capable of producing a sensitization response, a different vehicle should have been used for the challenge exposure.

b. The dermal sensitization study is unacceptable because it did not include a group of naive control animals. According to Buehler (1,2) "a group of previously unexposed control animals are challenged" and "the significance of reactions in the experimental group is based on intensity and incidence relative to reactions in the (two) control group(s)."

(3) The registrant must submit an acceptable dermal sensitization study performed with the subject product.

LABELING

(1) The appropriate signal word is CAUTION.

(2) The precautionary statements should read as follows:

Harmful if swallowed, absorbed through skin, or inhaled. Causes moderate eye irritation. Avoid contact with skin, eyes, or clothing. Avoid breathing vapor or spray mist. Wash thoroughly with soap and water after handling. Remove contaminated clothing and wash before reuse.

(3) The statements of practical treatment should read as follows:

IF SWALLOWED: Call a physician or Poison Control Center. Drink one or two glasses of water. Do not induce vomiting. Do not give anything by mouth to an unconscious person.

IF ON SKIN: Wash with plenty of soap and water. Get medical attention.

IF INHALED: Remove victim to fresh air. If not breathing give artificial respiration, preferably mouth to mouth. Get medical attention.

IF IN EYES: Flush with plenty of water. Call a physician if irritation persists.

NOTE: Further label revisions may be required following the submission of outstanding study data.

ACUTE TOXICITY PROFILE

Acute Oral	Category 3/Guideline
Acute Dermal	Category 3/Minimum
Acute Inhalation	Category 3/Guideline
Eye Irritation	Category 3/[redacted] Guideline
Dermal Irritation	Category 3/Guideline
Dermal Sensitization	Supplementary/Requested

REFERENCES

[1] Buehler, E.V. and Griffith, J.F. Experimental Skin Sensitization in the Guinea Pig and Man. Animal Models in Dermatology [H.I. Maibach, ed.] [1975] p. 56.

[2] Ritz, H.L. and Buehler, E.V. Planning, Conduct, and Interpretation of Guinea Pig Sensitization Patch Tests. Current Concepts in Cutaneous Toxicity, [Drill, V.A. and Lazar, P.] Academic Press, NY, NY. [1980] p. 25.

DATA REVIEW FOR ACUTE ORAL TOXICITY TESTING (§ 81-1)

Product Manager: 19
MRID No.: 420013-01
Testing Facility: Stillmeadow, Inc.
Author(s): Janice O. Kuhn
Species: Rat
Age: Young adult
Weight: 175-275 g
Source: Harlan Sprague Dawley
Test Material: Lorsban 30 Flowable
Quality Assurance (40 CFR §160.12): Present

Reviewer: M. Perry
Report Date: 1-4-91
Report No.: 7656-90

Conclusion:

1. **LD_{50} (mg/kg):** **Males** = 864 mg/kg
   Females = 514 mg/kg
   Combined = 661 mg/kg
2. **The estimated LD_{50} is** 514 mg/kg
3. **Tox. Category:** 3 **Classification:** Guideline

Procedure: The undiluted test material was administered to the fasted animals by way of oral intubation. Observations for clinical signs of toxicity and mortality were made daily. Body weights were recorded weekly.

Results:

Dosage mg/kg	(Number Killed/Number Tested)		
	Males	Females	Combined
350	---	0/5	0/5
500	0/5	2/5	2/10
700	2/5	5/5	7/10
1000	3/5	5/5	8/10

Symptoms & Gross Necropsy Findings: Clinical symptoms included activity decrease, ataxia, body tremors, chromodacryorrhea, and diarrhea. A necropsy revealed discolored kidneys, liver, lungs, and spleen.

DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (§81-2)

Product Manager: 19
MRID No.: 420013-02
Testing Laboratory: Stillmeadow, Inc.
Author(s): J. Kuhn
Species: Rabbit
Weight: 2.90-3.77 kg
Source: Ray Nichols
Test Material: Lorsban 30 Flowable
Quality Assurance (40 CFR §160.12): Present

Reviewer: M. Perry
Report Date: 1-2-91
Report No.: 7657-90

Summary:

1. **LC_{50} (mg/kg):** **Males** = --
Females = --
Combined = --

2. **The estimated LD_{50} is** > 2020 mg/kg

3. **Tox. Category:** 3 **Classification:**Minimum

Procedure: The undiluted test material was placed on the shaven backs of the animals and occluded for a period of twenty-four hours. Observations for clinical signs of toxicity and mortality were made at least daily. Body weights were recorded weekly.

Results:

Reported Mortality

DOSAGE mg/kg	(NUMBER KILLED/NUMBER TESTED)		
	Males	Females	Combined
2020	0/5	0/5	0/10

Symptoms & Gross Necropsy Findings: Clinical signs of toxicity included decreased urination, decreased defecation, and diarrhea. The gross necropsy revealed no observable abnormalities.

DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING (§81-3)

Product Manager: 19
MRID No.: 420013-03
Testing Laboratory: Stillmeadow, Inc.
Author(s): Mark Holbert
Species: Rat
Weight: 177-286 g
Source: Harlan Sprague Dawley
Test Material: Lorsban 30 Flowable
Quality Assurance (40 CFR §160.12): Present

Reviewer: M. Perry
Report Date: 5-20-91
Report No.: 7658-90

Summary:

1. LC_{50} (mg/kg): **Males** = 2.937 mg/L
   Females = 2.090 mg/L
   Combined = 2.408 mg/L

2. **The estimated LC_{50} is** 2.090 mg/L

3. **Mean Concentration:** --

4. **Tox. Category:** 3 **Classification:** Guideline

Procedure: All test animals were exposed for a period of four hours within a 500 L New York University design inhalation chamber. The aerosol was generated by an air atomizer and elutriated through a baffling chamber. The chamber concentration was determined analytically once per hour. Observations for clinical signs of toxicity and mortality were made at least daily. Body weights were recorded weekly.

Results:

Reported Mortality

Exposure Concentration mg/L	(NUMBER KILLED/NUMBER TESTED)		
	Males	Females	Combined
0.638	0/5	0/5	0/10
1.51	0/5	0/5	0/10
2.04	1/5	2/5	3/10
2/78	2/5	5/5	7/10

Symptoms & Gross Necropsy Findings: Clinical observations included activity decrease, ataxia, body tremors, catatonia, and diarrhea. The gross necropsy revealed discolored and swollen lungs, distended gastrointestinal tract, and fluid in the abdominal and thorasic cavities.

mg/l							
Nom Conc	Grav Conc	Analyt Conc	MMAD	GSD	Temp[C]	Hum%	Air Flow [l/m]
20.2	-----	0.638	3.139	2.310	70	69	133.1
38.6	-----	1.51	2.605	2.192	70	71	133.1
11.6	-----	2.04	2.726	2.201	72	90	134.5
44.6	-----	2.78	3.638	2.204	69	91	94.3

DATA REVIEW FOR ACUTE EYE IRRITATION TESTING (§81-4)

Product Manager: 19
MRID No.: 420013-04
Testing Laboratory: Stillmeadow, Inc.
Author(s): Janice Kuhn
Species: Rabbit
Sex: --
Weight: --
Source: Ray Nichols Rabbitry
Dosage: 0.1 ml
Test Material: Lorsban 30 Flowable
Quality Assurance (40 CFR §160.12): Present

Reviewer: M. Perry
Report Date: 12-27-90
Report No.: 7659-90

Summary:

1. **Toxicity Category:** 3
2. **Classification:** [redacted] Guideline

Procedure: A dose of 0.1 ml of undiluted test material was placed into one conjunctival sac of each animal. The lids were held together for approximately one second following administration. The animal eyes were examined at 1, 24, 48, and 72 hours.

Results:

Observations	(number "positive"/number tested)							
	Hour	Days						
	1	1	2	3	4	7	14	21
Cornea Opacity*	0/6	5/6	0/6	0/6				
Iris	0/6	0/6	0/6	0/6				
Conjunctivae								
Redness	0/6	0/6	0/6	0/6				
Chemosis	0/6	0/6	0/6	0/6				
Discharge**	6/6	0/6	0/6	0/6				

* Positive fluorescein staining considered positive
** Not considered "positive" reaction

Comments: Opacity (positive fluorescein staining) cleared between 24 and 48 hours.

DATA REVIEW FOR SKIN IRRITATION TESTING (§81-5)

Product Manager: 19
MRID No.: 420013-05
Testing Laboratory: Stillmeadow, Inc.
Author(s): Janice Kuhn
Species: Rabbit
Age: Young adult
Sex: --
Weight: --
Dosage: 0.5 ml
Test Material: Lorsban 30 Flowable
Quality Assurance (40 CFR §160.12): Present

Reviewer: M. Perry
Report Date: 1-4-91
Report No.: 7660-90

Summary:

1. **The Primary Irritation Index** = 1.6

2. **Toxicity Category:** 3

3. **Classification:** Guideline

Procedure: A dose of 0.5 ml of undiluted test material was administered to the shaven backs of six animals. The sites were covered with gauze and wrapped with semi-permeable dressing for a period of four hours. The test sites were observed at 3/4, 24, 48, and 72 hours, and on days 7, 10, 14, 17, and 21.

Results: The 72 hour evaluation period revealed grade one (n=3) and grade two (n=3) erythema. Grade one (n=3) and grade two (n=1) edema was also present at this period.

DATA REVIEW FOR SKIN SENSITIZATION TESTING (§81-6)

Product Manager: 19
MRID No.: 420013-06
Testing Laboratory: Stillmeadow, Inc.
Author(s): Janice Kuhn
Species: Guinea pig
Weight: 300-385 g
Source: Harlan Sprague Dawley
Test Material: Lorsban 30 Flowable
Positive Control Material: DNCB
Quality Assurance (40 CFR §160.12): Present

Reviewer: M. Perry
Report Date: 1-24-91
Report No.: 7661-90

Method: Modified Buehler

Summary:

1. **The sensitization potential of this product has not been determined.**

2. **Classification:** Supplementary

Procedure (Deviation From §81-6): See recommendations

Results: The animals were exposed to the test material (10% v/v) ten times over a three week period. Two weeks after the last induction exposure the animals were challenged on a naive site. A sensitizing reaction was produced by the test material (10% v/v) in ethanol. Following the first induction one of ten animals exhibited a dermal reaction (grade 1 erythema). Following the primary challenge five of ten animals exhibited dermal reactions (Grade 1 erythema).

Tox Chem. No. 219AA File Last Updated Current date 11-19-91

Study/Species/Lab/Study# Date	Material	MRID No.	Results	Tox. Cat.	Core Grade
Acute Oral: Rat, Stillmeadow, 7656-90, 1-4-91	Lorsban 30 Flowable (chlorpyrifos . . . 30.0%)	420013-01	Male LD_{50} = 864 mg/kg Female LD_{50} = 514 mg/kg	3	Guideline
Acute Dermal: Rabbit, Stillmeadow, 7657-90, 1-2-91	"	420013-02	LD_{50} > 2020 mg/kg	3	Minimum
Acute Inhalation: Rat, Stillmeadow, 7658-90, 5-20-91	"	420013-03	LC_{50} = 2.090 mg/l	3	Guideline
Eye Irritation: Rabbit, Stillmeadow, 7659-90, 12-27-90	"	420013-04	All eyes clear by 48 hrs	3	[redacted] Guideline
Dermal Irritation: Rabbit, Stillmeadow, 7660-90, 1-4-91	"	420013-05	Grade [redacted] two erythema present at 72 hrs (n=3)	3	Guideline
Dermal Sensitization: Guinea Pig, Stillmeadow, 7661-90, 1-24-91	"	420013-06	Not determined	—	Supplementary