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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM:

Subject: EPA Reg. No./File Symbol: 802-509 /
Lilly/Miller Moss-Out

From: Ian Blackwell, Biologist IDB 12/5/94
Precautionary Review Section
Registration Support Branch
Registration Division (7505W)

To: Joanne I. Miller, PM 23
Fungicide-Herbicide Branch
Registration Division (H7505C)

Thru: Thomas C. Ellwanger, Section Head
Precautionary Review Section
Registration Support Branch
Registration Division (7505W)

Applicant: The Chas. H. LILLY Co.
7737 N.E. Killingsworth
Portland, Oregon 97218

FORMULATION FROM LABEL:

Active Ingredient(s):::	% by wt.
Ferric sulfate, anhydrous	35.0
Inert Ingredient(s):	65.0
Total:	100.0%

Inert ingredient information may be entitled to confidential treatment

BACKGROUND: The Chas. H. LILLY Company has submitted a complete series of acute toxicity studies in support of Lilly/Miller "Moss-Out." These studies were submitted in response to the February 1993 Iron Salts RED. Cosmopolitan Safety Evaluation conducted these studies. The MRID numbers are 421717-01, 421717-02, 421717-03, 417587-01, 417587-02 and 417587-03.

The test material used in these six studies is identified as "Ferri-Floc". Ferri-Floc is the technical grade of the active ingredient used in the basic formulation of reg. no. 802-509. The registration product is a [redacted] of Ferri-Floc.

RECOMMENDATIONS:

1. The acute oral toxicity study is graded core-minimum data, but is acceptable to support the registration of this product. The study deficiencies are as follows:

   a. The study did not determine the LD_{50} for both sexes combined.
   b. The study did not determine the 95% confidence limits for the LD_{50}.
   c. The report did not state what phases of the study the quality assurance unit inspected/observed.

   The test material used was not the registration product. Reg. no. 802-509 is a [redacted] of the test material. Because the acute oral toxicity study is classified as toxicity category III, PRS will accept this study to support the reregistration of the product. The registration product could possibly produce toxicity category IV in an acute oral toxicity study due its being a [redacted] of Ferri-Floc. However, a change to oral toxicity category IV for this product would not change the signal word or add the necessity for personal protective equipment. Thus, it is felt that in this instance, the possible difference in toxicity categories will not pose a hazard. If the registrants wish to have this product placed into toxicity category IV for oral toxicity or to use oral toxicity category IV labeling for this product, they must submit an acceptable study proving that this product falls into acute oral toxicity category IV.

2. The acute dermal toxicity study is classified core-minimum data, but is acceptable to support the reregistration of the product. The study deficiency is that the report did not state what phase(s) of the study the quality assurance unit observed. If the registrants would like to have this study reconsidered, they must submit a statement expressing which phases of the study the quality assurance unit inspected.

   The acute dermal toxicity study conducted on Ferri-Floc is sufficient to support the reregistration of reg. no. 802-509. This study conducted on Ferri-Floc passed the limit test for

acute dermal toxicity studies (> 2000 mg/kg). As the technical product was placed into toxicity category III for acute dermal toxicity, PRS feels that the registration product would fall into toxicity category III or IV for acute dermal toxicity. It is unlikely, however, that the registration product would be placed into toxicity category IV for this study. The number of products that attempt to achieve toxicity category IV for acute dermal toxicity is small. However, a change to dermal toxicity category IV for this product would not change the signal word nor would it add a requirement for personal protective equipment.

3. The acute inhalation toxicity study is classified core-minimum data, but is acceptable to support the registration of the product. The study deficiency is that the report did not state which phase of the study the quality assurance unit observed.

This test material was placed into toxicity category III for acute inhalation toxicity. This study was found acceptable to support this product for the same reasons as the acute oral toxicity study. Please refer to number 1 above. It is possible that the registration product would fall into toxicity category IV for acute inhalation toxicity. If the registrants wish to have this product placed into category IV for inhalation toxicity or to use inhalation toxicity category IV labeling for this product, they must submit acceptable studies proving that the acute inhalation toxicity of this product falls into category IV.

4. The primary eye irritation study is classified core-minimum data, but is not acceptable to support the reregistration of reg. no. 802-509. This product is placed into toxicity category I for primary eye irritation. However, this is not because the study submitted was used to support it. With the test material being placed into toxicity category I, it is quite possible that the registration product (being a [redacted] of the test material) would not fall into category I. PRS does not bridge the data from a product in toxicity category I to support dilutions of that product.

The pH of this product is near 1. It is because the pH is so low that this product is placed into toxicity category I for primary eye irritation. As the product is placed into toxicity category I for eye irritation, PRS waives the requirement for a primary eye irritation study for this product.

The study deficiency is that the report did not state which phase(s) of the study the quality assurance unit observed/inspected. If the registrant will submit a statement explaining which phase(s) of the study the quality assurance observed, PRS will reconsider the classification of this study. However, it will still not be acceptable to support reg. no. 802-509.

5. The primary skin irritation study is classified core-minimum data, but is acceptable to support the reregistration of the product. The study deficiency is that the report did not specify which phases of the study the quality assurance unit inspected.

   Although the pH of this product is low enough to consider the registration product to be dermally corrosive, the results of the study conducted on the technical product falls into toxicity category IV. As such, having the registration product [redacted] of the test material) fall into a toxicity category other than IV is implausible.

6. The dermal sensitization study is classified supplementary data, but may be upgraded. The study deficiency is that the report did not specify the results of the positive control study. If the registrants wish to have this study reconsidered, they must submit the results from a positive control study conducted by Cosmopolitan Safety Evaluation within six months of dermal sensitization study F3082.

The acute toxicity profile for reg. no. 802-509 is currently:

acute oral toxicity	III	minimum
acute dermal toxicity	III	minimum
acute inhalation toxicity	III	minimum
primary eye irritation	I	minimum
primary skin irritation	IV	minimum
dermal sensitization		supplementary

LABELING:

1. The signal word is "DANGER", based on primary eye irritation.

2. The precautionary statements shall say:

   "Corrosive. Causes irreversible eye damage. Harmful if swallowed, inhaled or absorbed through skin. Do not get in eyes, on skin or on clothing. Avoid breathing dust or spray mist. Wear goggles, face shield or safety glasses. Wash thoroughly with soap and water after handling. Remove contaminated clothing and wash contaminated clothing before reuse."

3. The statements of practical treatment must say:

   "If in eyes: Hold eyelids open and flush with a steady gentle stream of water for 15 minutes. Call a physician."

   "If swallowed: Drink promptly a large quantity of milk, egg white, gelatin solution, or, if these are not available, large quantities of water. Avoid alcohol. Get medical attention. 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."

Note to Physician: Probable mucosal damage may contraindicate the use of gastric lavage.

4. This product is classified as an acute hazardous waste based on eye irritation. The following statement must appear on the label:

   "Pesticide wastes are acutely hazardous. Improper disposal of excess pesticide, spray mixture, or rinsate is a violation of Federal Law. If these wastes cannot be disposed of by use according to label instructions, contact your State Pesticide or Environmental Control Agency, or the Hazardous Waste representative at the nearest EPA Regional Office for guidance."

5. This product hits the trigger for restricted use due to eye irritation. The PM Team should decide if alternate labeling is sufficient to offset the need for restricted use classification and the hazards posed by this product.

6. This product hits the trigger for Child Resistant Packaging due to eye irritation. The PM Team should decide what course of action would best offset the hazards posed by this product.

7. Labeling revisions may be required upon the submission of the outstanding data.

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

Product Manager: 23
MRID No.: 421717-01

Reviewer: I. Blackwell
Study Completion Date: 1/7/92
Lab Project No.: A3251

Testing Facility: Cosmopolitan Safety Evaluation
Authors: Geoffrey Robbins

Quality Assurance (40 CFR §160.12): Included

Test Material: Ferri-Floc; "off-white granular powder/granules"

Species: Sprague-Dawley rats
Age: young adult
Sex: 15 males + 15 females
Weight: males = 264-284 g; females = 205-220 g
Source: laboratory colony

Conclusion:

1. **LD_{50} (mg/kg):** **Males** = 2102 mg/kg
Females = 1487 mg/kg
Combined = not determined

2. **Tox. Category:** III **Classification:** core-minimum

Procedure (Deviations from §81-1):
♪The combined LD_{50} for both sexes was not determined.
♪The study did not determine the standard of deviation for the LD_{50}s
♪The quality assurance unit did not state which phase(s) of the study they inspected.

Results:

Dosage (mg/kg)	(Number Killed/Number Tested)		
	Males	Females	Combined
1.25	0/5	0/5	0/10
1.77	0/5	5/5	5/10
2.5	5/5	5/5	10/10

Observations: Chromorhinorrhea; prostration, lethargy, depressed activity; yellow or brown perineal staining, constipation; ataxia.

Gross Necropsy: Hepatitic mottling, G.I. congestion, cyanosis of the nail beds; perineal staining.

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

Product Manager: 23 **Reviewer:** Ian Blackwell
MRID No.: 421717-02 **Study Completion Date:** 11/22/91
Study No.: B3251
Testing Laboratory: Cosmopolitan Safety Evaluation
Author: Geoffrey Robbins

Quality Assurance (40 CFR §160.12): Included

Test Material: Ferri-Floc; Ferric Sulfate; "off-white powder/ granules"

Species: albino rabbit
Weight: males = 2.5-3.0 kg; females = 2.5-2.6 kg
Age: young adult
Source: laboratory colony

Summary:

1. LD_{50} (mg/kg): **Males** > 2000 mg/kg
Females > 2000 mg/kg
Combined > 2000 mg/kg

2. **The estimated LD_{50} is greater than 2000 mg/kg of body weight.**

3. **Tox. Category:** III **Classification:** core-minimum

Procedure (Deviation From §81-2):
The report did not state which phase of the study was inspected by quality assurance.

Results:

Reported Mortality

DOSAGE	(NUMBER KILLED/NUMBER TESTED)		
	Males	Females	Combined
2000 mg/kg	0/5	0/5	0/10

Signs of toxicity: Erythema and edema.

Gross Necropsy Findings: No pathonomic signs.

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

Product Manager: 23 **Reviewer:** I. Blackwell
MRID No.: 421717-03 **Study Completion Date:** 12/23/91
Lab Project No.: C3251

Testing Laboratory: Cosmopolitan Safety Laboratory
Author: Geoffrey Robbins

Quality Assurance (40 CFR §160.12): Included

Test Material: Ferri-floc; Ferric Sulfate; "off-white powder /granules"
Concentration: nominal = 18.5 mg/L, gravimetric = 1.1 mg/L.

Species: rats, Sprague-Dawley derived
Weight: males = 242-267 g; females = 202-219 g
Age: young adult
Sex: 5 males + 5 females
Source: lab colony

Summary:

1. LC_{50} (mg/ℓ): Males > 1.1 mg/L
   Females > 1.1 mg/L
   Combined > 1.1 mg/ℓ
2. The estimated LC_{50} is greater than 1.1 milligram per liter.
3. MMAD: 2.75 µm
4. Tox. Category: III Classification: core-minimum

Procedure (Deviation From §81-3):
The report did not state which phase of the study was inspected by quality assurance.

Results:

Reported Mortality

Exposure Concentration	(NUMBER KILLED/NUMBER TESTED)		
	Males	Females	Combined
1.1 mg/L	0/5	0/5	0/10

Chamber Atmosphere				
Dose Level	MMAD	GSD	particles < 4 μm	particles < 1.7 μm
1.1 mg/L	2.75 μm	5.925 μm	57.65%	32.6%

Chamber Environment	
Chamber Volume	47.4 liters
Airflow	10 liters/min.
Temperature	76 °F
Target Relative Humidity	62-64%

Clinical Observations: yellow perineal staining; back covered with test material.

Gross Necropsy Findings: No pathonomic findings.

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

Product Manager: 23
MRID No.: 417587-01

Reviewer: Ian Blackwell
Study Completion Date: 12/2/90
Study No.: D3082

Testing Laboratory: Cosmopolitan Safety Evaluation, Inc.
Author: Geoffrey Robbins

Quality Assurance (40 CFR §160.12): Included

Test Material: Ferri Floc; "beige granules"
Dosage: 0.1 gram

Species: albino rabbit
Sex: 3 males + 3 females
Weight: 2.0-2.3 kilograms
Age: young adult
Source: laboratory colony

Summary:

1. **Toxicity Category:** I

2. **Classification:** core-minimum

Procedure (Deviations From §81-4):
)The appearance of ocular discharge (or lack thereof) was not reported.
)The report did not state which phase of the study was observed by quality assurance.

Results:

Observations	(number "positive"/number tested)							
	Hour	Days						
	1	1	2	3	4	7	14	21
Cornea Opacity	6/6	6/6	6/6	6/6	a5/6	---	---	---
Iris	6/6	*5/6	4/6	3/6	3/6	---	---	---
Conjunctivae								
Redness	0/6	4/6	5/6	5/6	6/6	---	---	---
Chemosis	6/6	6/6	6/6	6/6	6/6	---	---	---
Discharge	---	---	---	---	---	---	---	---

Comments: Scattered areas of palpebral conjunctiva white to yellow were observed. After the one hour observation, the irises of the test animals were not visible due to corneal opacity.
a-Corneal perforation was observed.

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

Product Manager: 23
MRID No.: 417587-02

Reviewer: Ian Blackwell
Study Completion Date: 12/1/90
Study No.: E3082

Testing Laboratory: Cosmopolitan Safety Evaluation, Inc.
Author: Geoffrey Robbins

Quality Assurance (40 CFR §160.12): Included

Test Material: Ferri-Floc; "beige granules"
Dosage: 0.5 gram moistened with 0.25 ml normal saline

Species: albino rabbit; New Zealand type
Age: young adult
Sex: 1 males + 4 females **Weight:** 2.0-2.6 kg
Source: laboratory colony

Summary:

1. **Toxicity Category:** IV

2. **Classification:** core-minimum

Procedure (Deviations From §81-5):
The report did not state which phase of the study was inspected by quality assurance.

Results: Three-quarters of an hour after unwrapping, 6/6 test animals displayed very slight erythema and 1/6 displayed very slight edema. Twenty-four and forty-eight hours after exposure, 4/6 test animals displayed very slight erythema. Seventy-two hours after exposure, no irritation was observed.

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

Product Manager: 23
MRID No.: 417587-03

Reviewer: I. Blackwell
Study Completion Date: 1/3/91
Study No.: F3082

Testing Laboratory: Cosmopolitan Safety Evaluation, Inc.
Author: Geoffrey Robbins

Quality Assurance (40 CFR §160.12): Included

Test Material: Ferri-Floc; "beige granules"
Positive Control Material: p-phenylenediamine

Species: albino guinea pig
Weight: 366-392 grams **Age:** young adult
Source: Camm Research Lab Animals

Method: Modified Buehler Method

Summary:

1. **This Product is / is not a dermal sensitizer.**

2. **Classification:** supplementary

Procedure (Deviation From §81-6):
The report did not include the results of the positive control study.

Procedure: An amount of 0.5g the test material moistened with 0.25 ml normal saline was applied to the exposure site under a non-allergenic pad, and wrapped with elastic bandage for 6 hours. The test site was rinsed with warm water if necessary. There was one induction treatment per week, over a period of three weeks, for a total induction treatments.

Results: Twenty-four hours after induction treatment #1, 2/10 test material-treated animals displayed very slight erythema . Twenty-four hours after induction #2, 3/10 test material-treat animals displayed very slight erythema. Twenty-four hours after induction #3, 7/10 test material-treat animals displayed very slight erythema. Twenty-four hours after challenge with the test material, 3/10 test animals displayed very slight erythema on virgin sites.

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ACUTE TOX ONE-LINER

1. PC CODE: 034902

2. CURRENT DATE: December 1, 1994

3. TEST MATERIAL: Ferric sulfate, anhydrous ... 71.4%

Study/Species/Lab/ Study#/Date	MRID No.	Results	Tox. Cat.	Core Grade
acute oral toxicity / rat / Cosmopolitan Safety Evaluation / A3251 / 1-7-92	421717-01	LD_{50} males = 2102 mg/kg females = 1487 mg/kg	III	M
acute dermal toxicity / rabbit / Cosmopolitan Safety Evaluation / B3251 / 11-22-91	421717-02	LD_{50} > 2000 mg/kg for both sexes	III	M
acute inhalation toxicity / rat / Cosmopolitan Safety Evaluation / C3251 / 12-23-91	421717-03	LC_{50} > 1.1 mg/l for both sexes	III	M
primary eye irritation / rabbit/ Cosmopolitan Safety Evaluation / D3082 / 12-2-90	417587-01	Corneal perforation in 1/6 and opacity in 5/6 on day 4.	I	M
primary skin irritation / rabbit / Cosmmopolitan Safety Evaluation / E3082 / 12-1-90	417587-02	Twenty-four and forty-eight hours after exposure, 4/6 displayed very slight erythema. No irritation by day 3.	IV	M
dermal sensitization / guinea pig / Cosmopolitan Safety Evaluation / F3082 / 1-3-91	417587-03			S

Core Grade Key:

G = Guideline
M = Minimum
S = Supplementary