4-2-93

10404

MEMORANDUM:

Subject: EPA Reg. No.: 3125-96

From: Mark J. Perry, Biologist MJP 3-31-93
Precautionary Review Section
Registration Support Branch
Registration Division (H7505W)

To: Robert J. Taylor, PM 25
Fungicide-Herbicide Branch
Registration Division (H7505C)

Thru: Thomas C. Ellwanger, Section Head E 4/2/93
Precautionary Review Section
Registration Support Branch
Registration Division (H7505W)

Applicant: Miles Inc.
P.O. Box 4913
Kansas City, MO

FORMULATION FROM LABEL:

	% by wt.
Active Ingredient(s): S,S,S-tributyl phosphorotrithioate	97.0
Inert Ingredient(s):	3.0
Total:	100%

BACKGROUND

Mobay Corporation has submitted an eye irritation study in support of the product DEF Technical, EPA Reg. No. 3125-96. The Registrant has also cited acute oral, acute dermal, dermal irritation and dermal sensitization studies performed with technical S,S,S-tributyl phosphorotrithioate. An inhalation study supporting this product was previously reviewed by PRS and found acceptable.

DEF Technical is used for formulation into end-use products and is composed of S,S,S-tributyl phosphorotrithioate (97%). The eye study was performed by Miles, Inc., and the MRID number is 424416-01. The acute oral, acute dermal, dermal irritation and dermal sensitization studies were performed by Mobay Corporation and the MRID numbers are 419549-03, 419549-02, 418963-03 and 416188-12, respectively.

RECOMMENDATION

The acute oral, acute dermal and eye irritation studies are acceptable as core guideline data. The dermal irritation and dermal sensitization studies are unacceptable.

1. PRS requires additional information before a decision on the acceptability of the dermal irritation study can be made. Following the submission of the requested information, this study will be considered for upgraded status.

•PRS requests that the testing laboratory explain how grade four edema was observed in the absence of any erythema.

•PRS requests a complete description of all effects observed during the evaluation of the dermal irritation study. Were any other dermal reactions, such as blanching or eschar, present at any time during the evaluations?

2. A new dermal sensitization study is required to support this registration. The subject dermal sensitization study is unacceptable for the following reasons:

• The concentration selected for induction was not sufficient to properly stimulate the animal immune system. For induction, a dose should be employed which produces mild to moderate irritation in order to ensure adequate exposure and enhance test sensitivity [2]. Only for primary challenge should the highest nonirritating concentration be used.

The highest nonirritating concentration is defined as that concentration which results in reactions no more severe than very faint erythema in two of four animals at 24 hours [1]. The challenge concentration employed in this study resulted in no erythema during the preliminary screen; such a concentration does not meet the criteria for the highest nonirritating concentration.

• The experimental animals should weigh between 300-350 g at the initiation of the sensitization study.

• A dose of 0.4 ml should be used for the induction and challenge exposures. The subject study employed 0.3 ml doses.

LABELING

1. The appropriate signal word is "Warning."

2. 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 and induce vomiting by touching back of throat with finger. Do not induce vomiting or 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.

3. The Precautionary Statements should read as follows:

May be fatal if swallowed or absorbed through skin. Harmful if inhaled. Avoid breathing vapor or spray mist. Do not get in eyes, on skin or on clothing. Wear protective clothing and rubber gloves. Wash thoroughly with soap and water before eating, drinking or using tobacco. Remove contaminated clothing and wash before reuse.

4. Additional label changes may be required following the submission of requested acute data.

ACUTE TOXICITY PROFILE

Acute Oral	Category 2/G
Acute Dermal	Category 2/G
Acute Inhalation*	Category 3/G
Eye Irritation	Category 4/G
Dermal Irritation	Supp
Dermal Sensitization	Supp

* See 5/19/92 PRS review of 3125-96

REFERENCES

1. Ritz, H.L. and Buehler, E.V. 1980. Planning, Conduct, and Interpretation of Guinea Pig Sensitization Patch Tests. Current Concepts in Cutaneous Toxicity, eds. V.A. Drill and P. Lazar, pp. 25-40. New York: Academic Press.

2. Robinson, M.K., Nusair, T.L., Fletcher, E.R., and Ritz, H.L. A review of the Buehler guinea pig skin sensitization test and its use in a risk assessment process for human skin sensitization. Toxicol., 61 [1990] 91.

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

Product Manager:25
MRID No.:419549-03
Testing Facility: Mobay
Author(s):L.P. Sheets
Species: Rat
Age: Young adult
Weight:199-350 g
Source: Sasco, Inc.
Test Material: Technical grade Tribufos (DEF)
Quality Assurance (40 CFR §160.12): Present

Reviewer:M. Perry
Report Date:5/20/91
Report No.:90-012-ES

Conclusion:

1. LD_{50} (mg/kg): **Males** = 435 mg/kg
   Females = 234 mg/kg
   Combined = --
2. **The estimated** LD_{50} **is** 234 mg/kg (183-296mg/kg)
3. **Tox. Category:** II **Classification:**Guideline

Procedure: The fasted test animals were dosed (as indicated below) by gavage with the test material in corn oil. The animals were observed for mortality and signs of toxicity at least daily during the 14 day observation period. Body weights were recorded just prior to treatment and on days 7 and 14.

Results:

Dosage mg/kg	(Number Killed/Number Tested)		
	Males	Females	Combined
192	---	0/5	0/5
235	---	4/5	4/5
294	0/5	4/5	4/10
429	3/5	---	3/5
552	4/5	---	4/5

Symptoms & Gross Necropsy Findings: decreased activity, lacrimation, lacrimal stain, nasal discharge and nasal stain were observed following treatment. Animals found dead during the study exhibited fluid and dark areas in the stomach and duodenum as well as pale liver. No abnormalities were observed among animals surviving until study termination.

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

Product Manager:25
MRID No.:419549-02
Testing Laboratory: Mobay
Author(s):L.P. Sheets
Species: Rabbit
Weight:1.92-2.40 kg
Source: Small Stock Industries
Test Material: Technical grade Tribufos (DEF)
Quality Assurance (40 CFR §160.12): Present

Reviewer:M. Perry
Report Date:5/31/91
Report No.:90-025-FE

Summary:

1. LC_{50} **(mg/kg):** **Males** = --
Females = --
Combined = 1093 mg/kg

2. **The estimated** LD_{50} **is** 1093 mg/kg

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

Procedure: The undiluted test material was applied to the clipped exposure sites of the animals and occluded for a period of 24 hours. The animals were observed for mortality and signs of toxicity at least daily during the 14 day observation period. Body weights were recorded on day of treatment and on days 7 and 14.

Results:

Reported Mortality

DOSAGE mg/kg	(NUMBER KILLED/NUMBER TESTED)		
	Males	Females	Combined
500	0/5	0/5	0/10
1000	2/5	2/5	4/10
2000	5/5	5/5	10/10

Symptoms & Gross Necropsy Findings: Tremors, muscle fasciculations, decreased motor activity, ataxia and diarrhea were observed in some animals during the study period. A gross necropsy revealed reddened thymus and dark perianal stain in males and females as well as pale areas in small intestines and fluid in abdominal cavity.

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

Product Manager:25
MRID No.:424416-01
Testing Laboratory: Miles
Author(s):L.P. Sheets, S.D. Phillips
Species: Rabbit
Sex: Male
Weight:NA
Source: Small Stock, Industries
Dosage:0.1 ml
Test Material: Technical Grade Tribufos
Quality Assurance (40 CFR §160.12): Present

Reviewer:M. Perry
Report Date:3/31/92
Report No.:91-335-MN

Summary:

1. **Toxicity Category:**IV

2. **Classification:**Guideline

Procedure: A 0.1 ml dose of the test material was placed into one conjunctival sac of each animal and the eyelids were held together for approximately one second. The test eyes were examined for 72 hours to 7 days.

[redacted]

Results:

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

* Not considered "positive" reaction

Comments: Since no "positive" reactions were reported, a category IV grade has been assigned.

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

Product Manager:25
MRID No.:418963-03
Testing Laboratory: Mobay Corp.
Author(s):L.P. Sheets
Species: Rabbit
Age: Adult
Sex:male
Weight:NA
Dosage:0.5 ml
Test Material: Technical grade Tribufos (DEF)
Quality Assurance (40 CFR §160.12): Present

Reviewer:M. Perry
Report Date:4/30/91
Report No.:90-325-FS

Summary:

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

2. **Toxicity Category: --**

3. **Classification:**Supp

Procedure: A dose of 0.5 ml of test material was applied to the clipped exposure sites and occluded for a period of four hours. Dermal evaluations were performed at 1, 24, 48, and 72 hours as well as at 7 and 14 days.

Deviation from §81-5: See recommendations

Results: Grade 2 erythema was observed in all animals during the first 24 to 48 hours following exposure. Grade 1 through 3 edema was also reported in all animals and cleared by day 7. Grade 4 edema was observed in 2 test animals.

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

Product Manager:25
MRID No.:416188-012
Testing Laboratory: Mobay
Author(s):L.P. Sheets
Species: Guinea pig
Weight:259-339 g
Source: Sasco
Test Material: Technical grade Tribufos (DEF)
Positive Control Material:DNCB
Quality Assurance (40 CFR §160.12): Present

Reviewer:M. Perry
Report Date:8/17/90
Report No.:90-324-GK

Method: Buehler

Summary:

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

2. **Classification:**Supplementary

Procedure: The test animals were induced at clipped exposure sites with a 10% concentration of the test material once a week for three weeks. Each application was occluded and contact was maintained for six hours. Following a two week rest period, the test group was challenged in the same manner as the induction treatments except with a 1.0% concentration and at a naive site. A group of naive control animals was also employed in the study.

Deviation From §81-6: See recommendations

Results: No erythema or edema was reported in the test animals during the induction treatments. Slight, barely perceptable erythema was reported in 8 of 15 animals at the 24 hour challenge evaluation.

Tox Chem. No. 74801 File Last Updated Current date 1/7/93

Study/Species/Lab/Study# Date	Material	MRID No.	Results	Tox. Cat.	Core Grade
ACUTE ORAL, RAT, MOBAY, 90-012-ES, 5/20/91	Technical Tribufos	419549-03	♀ LD50= 234 mg/kg ♂ LD50= 435 mg/kg	II	G
ACUTE DERMAL, RABBIT, MOBAY, 90-025-FE, 5/31/91	"	419549-02	LD50= 1093 mg/kg	II	G
EYE IRRITATION, RABBIT, MOBAY, 91-335-MN, 3/31/92	"	424416-01	No positive scores	IV	G
DERMAL IRRITATION, RABBIT, MOBAY, 90-325-FS, 4/30/91	"	418963-03	Grade 2 erythema and grade 3-4 edema	---	S
DERMAL SENSITIZATION, GUINEA PIG, MOBAY, 90-324-GK, 8/17/90	"	416188-12	Not determined	---	S