5-31-95

MEMORANDUM

Subject: EPA Reg. #: 618-96/97/98 Abamectin 0.15 EC

To: George Larocca, PM # 13 Attn: Linda Arrington
Insecticide-Rodenticide Branch
Registration Division (7505C)

FROM: David L. Ritter, Toxicologist
Registration Support Branch
Precautionary Review Section
Registration Division (7505W)

DLR 5-31-95

Registrant: Merck & Co., Inc.
PO Box 450
Three Bridges NJ 08887-0450

Action Requested:

1. Review acute dermal toxicity study and dermal sensitization study.

2. Consider waiving requirement for dermal irritation study.

PRS Response:

1. Previously submitted data were reviewed in the W. Woodrow memorandum of 3/3/92. He found that the submitted dermal LD_{50} study and the dermal sensitization study were CORE Supplementary. The replacement studies are reviewed below.

   In addition, studies using MK-0936 Citrus Spray Formulation were reviewed by CDFA (R.L. Morgan, Ph.D., 5/6/91) and the dermal irritation study was determined to be TOX III and was acceptable for the purpose of CA registration.

   The replacement studies have been reviewed and the DERs are attached.

   The acute dermal study yielded a TOX category of III based on a limit assay LD_{50} > 2000 mg/kg. The dermal sensitization showed the product is a dermal sensitizing agent. Both studies were classified "Acceptable".

The acute toxicity data base for these products is complete and is summarized here:

Acute Toxicity Data Requirements (40 CFR §158.340). Pesticide Assessment Guidelines, Subdivision F. Hazard Evaluation: Human and Domestic Animals. (1982; revised 1984).

Data Required	MRID #	Toxicity Category	Classification
Acute Oral (§81-1)*	420203-01	II	A
Acute Dermal (81-2)	420798-01	II	A
Acute Dermal (81-2)	429836-01	III	A
Acute Inhal. (81-3)	420800-01	III	A
Eye Irr. (§81-4)	409125-01	II	A
Dermal Irr. (§81-5)**		III	A
Dermal Sens. (§81-6)	429836-02	Sens. GPMT	A

* Woodrow, 3/3/92
** CDFA, 5/6/91

Precautionary Labeling Review:

See the recommendations in the Woodrow memorandum of 3/3/92.

Add the following sentence to the Precautionary Statement:

"Prolonged or frequent repeated skin contact may cause allergic reactions in some individuals".

DATA EVALUATION RECORD FOR DERMAL TOXICITY TESTING §81-2

Product Manager (PM): 13 EPA Reg. No.: 618-96/97/98

Reviewer: David L. Ritter, Toxicologist DLR 5-31-95

MRID No.: 429836-01

Testing Laboratory: Merck Research Laboratories
West Point PA 19486

Title Of Report: Acute Dermal Toxicity Study in Rabbits

Date of Report: 9/9/93 Lab. No.: TT #93-2592

Author(s): Walter J. Bagdon Ph.D.

Species: New Zealand white rabbit Sex: 5M + 5F
Wt.: 2.57 - 2.91 kg

Source: Hazleton Research Prods., Denver PA

Test Material: MK-0936 0.15 Emulsifiable (Abamectin)

Dosage: 2000 mg/kg applied topically.

Quality Assurance (40 CFR, Section 160.12): Acceptable

Summary: LD_{50} M + F > 2000 mg/kg

Toxicity Category: III Classification: Acceptable

Procedure (Deviation From Series 81-2):

Standard laboratory animal husbandry and GLP were observed.

Animals were weighed initially, and on days 8 and 14.

Animals were clipped free of dorsal hair 24 hours prior to application. 2000 mg/kg undiluted Test Article was applied topically under a gauze patch to an area of approximately 10% body surface area over the dorsolateral surface. The test sites were then secured with occlusive dressings. Rabbits were fitted with Elizabethan collars.

After 24 hours the dressings were removed and the test sites cleansed with water.

Animals were observed for effects at day 1, then once daily thereafter for 14 days except for days 4, 5, 6, 12 and 13.

Animals were killed by pentobarbital injection on day 15.

Results:

No compound-related signs were reported.

No effect on weight-gain was reported.

There was no mortality.

REPORTED MORTALITY

DOSAGE MG/KG	MALES No.Dead/No. Exposed	FEMALES No. Dead/No. Exposed	COMBINED No. Dead/No. Exposed
2000 mg/kg	0/5	0/5	0/10

DATA EVALUATION RECORD FOR DERMAL SENSITIZATION TESTING §81-6

Product Manager (PM): 13 EPA Reg. No.: 618-96/97/98

Reviewer: David L. Ritter, Toxicologist 0625-3195

MRID No.: 429836-02

Testing Laboratory: Laboratoires Merck Sharp Dohme-Chibret
Centre de Recherche
Riom France

Title Of Report: Guinea Pig Sensitization Test

Date of Report: 8/10/93

Lab. No.: TT #93-615-0

Author(s): G. Durand-Cavagna

Species: Hartley albino guinea pig Sex: 32 F Wt.: 330 - 390 gm

Source: Charles River, France

Test Material: MK-0936 0.15 Emulsifiable (Abamectin)

Quality Assurance (40 CFR, Section 160.12): Acceptable

Summary:

The vehicle and the Test Article induced strong sensitizing responses in this assay. The product is a dermal sensitizer.

Classification: Acceptable.

Procedure (Deviation From §81-6): Magnusson & Kligman Guinea pig maximization test

Three groups were used: 10 or the control group; 11 for the vehicle control group (VC) and 11 pigs for the Test Group.

Induction Phase:

On day one the animals were clipped free of fur over ca 4 x 6 cm of the dorsum. Each animal was given 2 0.1 ml intradermal injections, one on either side of the dorsal midline.

The control group received Freund's Complete Adjuvant (FCA) in distilled water (DW) 50/50%.

The VC group received vehicle (Test Article minus AI) diluted with FCA 50/50%.

The Test Group received Test Article 50/50% with FCA.

On day 7 all animals were clipped and were pretreated topically with 400 mg of 10% sodium lauryl sulfate in petrolatum.

On day 8, 2 x 4 cm patches of filter paper covered with aluminum foil containing 0.3 ml saline (Control Group); 0.3 ml of vehicle (VC group) and 0.3 ml of Test Article was given to the Test Group.

Patches were affixed and remained *in situ* for 48 hours.

Challenge Phase:

On day 22 the animals were clipped over the right and left flanks.

The VC group and Test Group received a 2x2 cm patch of filter paper/aluminum foil on left flank.

The Control Group received 2 papers containing 0.15 ml saline (right flank) and 2 patches containing either 0.15 VC (left anterior flank) or 0.15 ml Test Article (left posterior flank) containing 0.15 ml saline. The patches were secured for 24 hours.

The challenge sites were evaluated using a scoring system of 0 - 3 at 24 and 48 hours after patch removal.

Results:

The Control Group showed 1/10 animal with a "1" reading at 24 hours and a "2" at 48 hours for the VC application site.

The VC group showed 7/11 "1" responses at 24 hours; 7/11 "1" and 2/11 showed "2" at 48 hours.

The Test Article group showed 10/11 "1" at 24 hours; 8/11 "1" and 2/11 "2" at 48 hours.

Conclusions:

The vehicle and the Test Article induced strong sensitizing responses in this assay. The product is a dermal sensitizer.

Classification: Acceptable.

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ACUTE TOX ONE-LINER

1. PC CODE: 122804; Abamectin

2. CURRENT DATE: 5/17/95

3. TEST MATERIAL: Avid 0.15 EC

4. EPA Reg. #: 618-96/97/98

Study/Species/Lab/ Study#/Date	MRID No.	Results	Tox. Cat.	Core Grade
Acute dermal/rabbit/ MRL*/TT #93-2592/ 9-9-93	429836-01	LD_{50} > 2000 mg/kg	III	A
Dermal sens./guinea pig/MRL/TT #93-615-0/8-10-93	" -02	Sensitizer GPMT	---	A

* Merck Research Laboratories
West Point PA 19486

0025-31-95

Core Grade Key:

A = Acceptable
U = Unacceptable
S = Supplementary

EPA Reg #618-96

TO: Gary Sprock, Registration Specialist
Pesticide Registration Branch

FROM: Medical Toxicology Branch

Date: 4/2/91
Revised: 5/6/91

PRODUCT REGISTRATION RECOMMENDATION SHEET

Formulated Product Name: AVID 0.15 EC, ZEPHYR 0.15 EC
Chemical Code #: 2254 **ID #:** 127960
EPA Reg. #: 618-96 **SB 950 #:** Not assigned
Document #'s: 50406-173
Company Name: Merck & Co., Inc.

RECOMMENDATION:
Submitted as a Section 3 Label Amendment.

Data reviewed are adequate for a complete toxicologic evaluation. Although these data are adequate for the current evaluation, the final reports as indicated by the USEPA letter dated 2/27/91 are required by 9/10/91.

The product label does not identify the Category II acute oral toxicity hazard or the Category III acute inhalation toxicity hazard as indicated by the data reviewed.

The label amendment is not accepted at this time.

Ronald L. Morgan, Ph.D.
Staff Toxicologist

5-6-91
Date

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TO--File: Registration **Registration Specialist: Gary Sprock**
Branch: Registration
FROM--Medical Toxicology

DATA PACKAGE SUMMARY AND RECOMMENDATION SHEET

Active Ingredient: Avermectin
Formulated Product Name: AVID 0.15 EC, ZEPHYR 0.15 EC
Formulation: 1.9% Avermectin, 98.1% inert ingredients
Chemical Code #: 2254 **ID #:** 127960
EPA Reg. #: 618-96 **SB 950 #:** Not assigned
Document #'S: 50406-173
Company Name: Merck & Co., Inc.

SUMMARY: ("CDFA One-liners" from each study worksheet,significant information not mentioned in worksheets, other pertinent information for ongoing review or registration. Attach additional sheets if needed)
The data submitted for MK-0936 Citrus Spray Formulation are considered bridgeable to the subject product. The test article and the subject product are nearly identical. Since no acute dermal toxicity study for this test article was submitted, the acute dermal toxicity study for the technical a.i. will be used to determine this hazard for the subject product.

MK-0936 Citrus Spray Formulation Acute Toxicity Categories

Acute Oral LD50	II
Acute Dermal LD50	None submitted
Acute Inhalation LC50	Unacceptable (see conclusions)
Eye Irritation	III
Dermal Irritation	III

MK-0936 Citrus Spray Formulation Acute Toxicity Studies

Acute Oral LD50
50406-173; 96569; Acute Oral Toxicity, 811; rat; Merck Institute for Therapeutic Research, West Point, PA, 1/23/91; MK-0936 Citrus Spray Formulation, L-676,863-304Y (Lot #2), 2.21% a.i.; 0.24, 0.38, 0.61, 0.98 and 1.56 g/kg, 10/sex/dose; Mortalities - male 0, 0, 10, 10 and 10, female 0, 2, 6, 9 and 10, respectively; Toxic signs included tremors, decreased activity, loss of righting reflex, red material around eyes and/or nose, vocalization, salivation, urine staining and gasping; No treatment-related necropsy findings were observed; Male LD50 = 0.485 g/kg, female LD50 = 0.561 g/kg, Combined male & female LD50 = 0.527 g/kg; Toxicity Category II, Acceptable. (Morgan, 4/2/91)

Acute Dermal LD50
None submitted

Acute Inhalation LC50
50406-173; 96978, 92714; Acute Inhalation Study-range finding; 813; Rat; Bio-Research Laboratories Ltd, Senneville, Quebec, Canada; AVID 0.15 EC (MK-0936 EC); Bio-Research # 90327R; 4 animals/sex/group; Exposure Concentrations (gravimetric): 2.26, 2.53 (female only), 2.82, 3.02, 3.24, 4.18 (male only), 4.53 (male only) mg/l, vehicle control: 3.14, 4.59 mg/l; MMAD (+ GSD) 2.1 (+ 1.8) µm (performed once prior to study); Mortality: 2.26 (M:0/4,F:1/4), 2.53 (F:0/4), 2.82 (M:1/4,F:3/4), 3.02 (M:1/4,F:3/4), 3.24 (M:2/4,F:4/4), 4.18 (M:3/4), 4.53 (M:3/4); Observations (at the time of exposure): muzzle and

urogenital staining, lack of balance, lethargy, tremors; (Vehicle): piloerection, rapid respiration, muzzle and urogenital staining; no necropsy data provided; Study performed for the purpose of determining an acceptable range of doses for a guideline study; Study unacceptable and not upgradeable (a minimum of 5 animals/sex/group, particle sizing of the aerosol and observation of the animals for 14 days are required). (Moore, 4/26/91)

Eye Irritation

50406-173; 96571; Eye Irritation, 814; rabbit; Merck Institute for Therapeutic Research, West Point, PA, 1/24/91; MK-0936 Citrus Spray Formulation, L-676,863-304Y (Lot #2), 2.21% a.i.; 0.1 ml/eye, 5/sex/dose, 6 nonrinsed eyes and 4 rinsed eyes; Irritation for nonrinsed eyes - at 24 hours: grade 1 iritis (3 rabbits) and grade 1-3 conjunctival irritation (6 rabbits), at 7 days: grade 1 conjunctival (3 rabbits), all irritation cleared by day 11; Category III, Acceptable. (Morgan, 4/2/91)

Dermal Irritation

50406-173; 96570; Dermal Irritation, 815; rabbit; Merck Institute for Therapeutic Research, West Point, PA, 1/24/91; MK-0936 Citrus Spray Formulation, L-676,863-304Y (Lot #2), 2.21% a.i.; 0.5 ml/site (2 ml/rabbit), 3/sex/dose, 24 hour exposure, occluded, 2 sites abraded and 2 sites intact; no mortalities or toxic signs; irritation: Intact Skin Sites at 24 hours: grade 1-2 erythema (6 rabbits) and grade 1 edema (5 rabbits), at 72 hours: grade 1-2 erythema (4 rabbits) and scale formation (1 rabbit), at 7 days: grade 1 erythema (2 rabbits) and scale formation (1 rabbit), at 14 and 21 days: scale formation (1 rabbit); Category III, Acceptable. (Morgan, 4/2/91)

Avermectin Technical Toxicity Categories

Acute Oral LD50	I
Acute Dermal LD50	III
Acute Inhalation LC50	None submitted
Eye Irritation	III
Dermal Irritation	IV

Avermectin Technical Toxicity Studies

Acute Oral LD50

50406-008; 46614; Acute Oral Toxicity, 811, rats; Merck Sharp and Dohme Research Labs; 8-10-81; (Avermectin B_1 Techn. 91.4%); dose levels 6.67, 10.00, 15.00, 22.50, and 33.75 mg/kg; 10 animals/sex/dose; no treatment related changes; gross and microscopic changes were considered spontaneous findings; LD_{50} (male) = 8.7 mg/kg (C.I. 4.4-11.8) LD_{50} (female) = 12.8 mg/kg (C.I. 10.4-14.9); Category I; acceptable. (Berliner, 7/30/86)

Acute Dermal LD50

50406-008; 46615; Acute Dermal Toxicity, 812, rabbits; Merck Sharp and Dohme Research Labs; 2-7-84; (MK-0936 Techn. 94.0%); dose level 2.12 g/kg; sixth day 9/10 animals lethargic, ataxia, abnormal head movements, tremors, bradypnea and disorientation; at termination all rabbits had a 21-37% weight loss from initial body weights; no mortalities; LD_{50} (M/F)>2.12 g/kg; Category III; acceptable. (Berliner, 7/30/86)

50406-008; 46616; Acute Dermal Toxicity, 812, rabbits; Merck Sharp and Dohme Research Labs; 3-16-83; (MK-0936 Techn. Avermectin B_1, 91.4%); dose levels of 100, 200, 400, 800 and 1600 mg/kg; majority of surviving rabbits at all dose levels had 1-30% weight loss; on day 3, 7/8 rabbits of the 1600 mg/kg group exhibited signs of ataxia, occasional tremors and loss of righting reflex (1-2 rabbits in 200, 400, and 800 mg/kg dosage groups had similar signs at 4 to 11 days after treatment); no evidence of toxicity at doses less than 200 mg/kg and essentially nonirritating to the rabbit's skin; acceptable. Berliner, 7/30/86.

Acute Inhalation LC50
None submitted

Eye Irritation
50406-008; 46617; Eye Irritation, 814, rabbits; Merck Sharp and Dohme Research Labs 8-11-81; (Avermectin B_1 Powder-Techn. Grade, Avermectin B_1 Formulation-L-676, 863-27U03, and vehicle formulation); dose level 0.1 ml; 3M/3F unwashed eyes; all eyes cleared by 48 hours; Category III; Acceptable. (originally reviewed as unacceptable, Berliner, 7/31/86; submission of additional data, 056 #52041, makes study acceptable, 1/6/87 Patterson)

Dermal Irritation
50406-008 46618; Dermal Irritation, 815, Rabbits; Merck Sharp and Dohme Research Labs, 8-11-81; (Avermectin B_1 Powder-Techn., Formulated, and vehicle); dose levels 0.5g, 0.5ml, and 0.5ml, respectively; all animals had zero scores at 48 hours; Category IV; acceptable. (Berliner, 8/1/86)

CONCLUSIONS: Are data adequate to support registration?

Data reviewed are adequate for a complete toxicologic evaluation. The submitted acute inhalation toxicity study is unacceptable. However, there are adequate data in this study to indicate a Category III acute inhalation toxicity hazard.

RECOMMENDATIONS: What type of registration action is being requested? In case of ongoing registration, register or do not register? What other specific studies or data are requested?

Submitted as a Section 3 Label Amendment.

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The product label does not identify the Category II acute oral toxicity hazard or the Category III acute inhalation toxicity hazard as indicated by the data reviewed.

The label amendment is not accepted at this time.

Ronald L. Morgan, Ph.D.
Staff Toxicologist

5-6-91
Date