US EPA ARCHIVE DOCUMENT

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

FEB 19 1991

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Reg. No./File Symbol 618-97
MK-0936 Citrus Spray Formulation

FROM: Lucy ~. Markarian 2/12/91 LM
Precautionary Review Section E 2/19/91
Registration Support Branch
Registration Division (H75-05C)

TO: George La Rocca (PM 15)
Insecticide - Rodenticide
Registration Division (H75-05C)

APPLICANT: Merck Sharp & Dohme
Hillsborough Road, Three Bridges
New Jersey 08887

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
Avermectin B_1	2.0%
Inert Ingredient(s):	98.0%
Total	100.0%

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BACKGROUND:

Merck Sharp and Dohme has presented the drafts of an oral Toxicity Test, Two sets of eye irritation studies and a dermal irritation study to support a change of formulation of Three of Their products: Aud (EPA 618-[illegible]), Zephyr (EPA 618-97), and Agri-Mek (EPA 618-98). All These products have the same composition. The proposed change is to replace [redacted] of the [redacted] in the inerts with [redacted]. The new formulation, MK-0936, is used for the Test material in the presented studies. The Toxicity profile of the existing old formulation is as follows:

Acute Oral Toxicity	LD_{50} > 5.0 g/kg	Catagory IV
Acute Dermal Toxicity	LD_{50} > 2.0 g/kg	catagory III
Acute Inhalation Toxicity	LC_{50} > 1.062 mg/L	catagory IV
Primary Eye Irritation	Eye irritant. opacity clear on day 14	catagory II
Primary Dermal Irritation	moderate irritant clear by day 7	catagory III
Not a sensitizer		

Previously Merck Sharp + Dohme had requested the evaluation of Two published papers That were about the acute Toxicity of [redacted]. After This review it was recommended That studies be submitted in all areas of toxicity, because [redacted] was reported to be able to enhance penetration and cause CNS Toxicity. Additionally the synergistic effects of This additive with the components of the formulation was not known.

In submitting the preliminary Test Merck Sharp + Dohme claims That The toxicity catagories are not likely to change and the signal word "warning" on the label would still be sufficient.

INERT INGREDIENT INFORMATION IS NOT INCLUDED

RECOMMENDATION:

The presented draft for the oral study is rated Supplementary data, but may be upgraded by supplying the following information.

1. The dosage levels are expressed in ml/kg, presumably due to the liquid state of the formulation. The report enumerates all the ingredients in their respective percentages but it is not established that each ml is equivalent to a gram. As the Toxicity catagory is determined by mg per kg, or gram per kilogram, and the specific gravity of the formulation, or vehicle is not presented, the applicant must express the dosage levels in grams or milligrams. If the specific gravity of the formulation is less than one (1) it could mean a lower Toxicity catagory. It is particularly important in this case, because the lower confidence limit in the combined LD_{50} calculations is already in catagory II.

2. The animals were not fasted prior to intubation as stated in the guidelines. The applicant must explain why this was not done. Fasted animals are routinely used by laboratories in good standing. Additionally not fasting the animals may make a difference in the manifestation of Toxicity as a full or partially full stomach will make a difference in the rate of absorption and delivery time to the target organs.

3. The males were over the weight limit stated in the guidelines. There is a small difference in the sexes in the expression of Toxicity. It is questioned if this difference is genuine or attributable to the weight of the males. Weight is an established varient in the expression of Toxicity.

INDEX INCREDIBLY INFORMATION IS NOT INCLUDED

Two sets of studies are presented for consideration in eye irritation. The first set includes a study using Test material L 676.863-304T the complete [redacted] formulation MK-0936 and a simultaneous study using the vehicle in the formulation identified as L 930-780-00E. Each of these have been tested in both unwashed and washed eyes. The washed eyes are not required by the regulations. Both are core minimum data for the following reason

1. Evaluation of eyes at 15 minutes is not meaningful because enough time has not elapsed to make a more than transient difference, by the mere presence of a foreign material, of the eye. The effect may or may not be a toxic manifestation.
2. One hour observation is not made. This would have been more meaningful. The two hour observation may be substituted for this purpose
3. At 24 hrs, it is not stated if the presence or absence of opacity is confirmed by fluorescein dye. Minor lesions unobserved otherwise can be identified by this method. Opacity is recorded at 48 hrs through Day 4 in the group treated with vehicle only. The likelyhood of the same vehicle causing eye irritation in the complete formulation is present. This could have been established with certainty by using fluorescein. This was the case.
4. It is not clear how any observation was correctly made with the presence of Grade 4 chemosis when the manipulation of the eye is almost impossible. If there was opacity it could not have been successfully observed through closed eyelids.

5. The meaning of "white mucoid discharge" is not clear. Whether This discharge is made up of purulent material or it is due to sloughing tissue needs to be clarified. The Grade 1 rating of discharge at the intervals at which This "white mucoid discharge" appears seems underrated (48 hrs Animal 308)

The second set includes a study using L 676, 863-312Y [redacted] formulation) and a simultaneous study using L 676, 863-313A [redacted] formulation) both in the same vehicle and both Tested in unwashed + washed eyes. As stated before washed eyes are not required by regulations. Also as previously stated 15 minute evaluations are not meaningful, and the observations at 2 hrs in the presence of Grade 4 chemosis cannot be considered to be too conclusive. Also the corneal observations at 24 hrs do not appear to be confirmed by fluorescein dye. The reasons for all this is explained previously.

The study conducted with the [redacted] formulation (L-676-863-312Y) is not extended beyond 14 days to prove That opacity, conjunctival redness and corneal anesthesia were reversible. Therefore The Test could not decide if the Test material was in category I or II and consequently rated as supplementary data

The study conducted with the [redacted] formulation (L 676-863-313A) is considered core minimum data, for the reasons stated above, but accepted as supporting

INERT INGREDIENT INFORMATION IS NOT INCLUDED

The Dermal irritation study is also considered core minimum data, but acceptable.

According to the guidelines Abraded sites are not required. The reason for the core minimum rating is as follows:

Applications must be made at a 6cm² area rather than a 5x5cm site according to the guidelines.

Exposure is to be for 4 hrs instead of 24.

Reading of the sites are to be at 1 hr, 24, 48 & 72 hrs and extended if grade 2 or higher reaction is observed at any one site until such time as the reaction is considered unremarkable.

Primary indices must be calculated based on the numerical values obtained at 1, 24, 48, & 72 hrs

The results do not indicate that the irritation is due to the vehicle, as the primary irritation index of the complete formulation is higher than the primary irritation index of the vehicle, as it is concluded by the author.

The presented studies so far do not indicate conclusively that the toxicity of the new formulation is about the same as the old formulation. Indications from the oral study is that the oral toxicity is higher than before, even when animals were intubated unfasted ("food not withheld") The eye irritation study using the [redacted] may be in catagory I. The study was not extended to 21 days to confirm this

INERT INGREDIENT INFORMATION IS NOT INCLUDED

There is not enough evidence to show that the toxicity profile of the new formulation is comparable to the toxicity profile of the old formulation. It cannot be assumed that the new formulation will have no more deleterious effects than the old formulation if tested in dermal toxicity or inhalation, because the oral toxicity appears to be changing and the new additive may very well change the dermal and inhalation toxicity due to its ability to enhance absorption, and possible neurotoxic effects.

The following are the recommendation after the evaluation of the submitted drafts;

1. Merck Sharp and Dohme have to clarify if they are proposing to use the [redacted] formulation (L.676.863-304Y) or the [redacted] formulation (L 676.863-313A) for their formulation or whether they intend to use both.

2. Depending on the formulation to be used they must supply either

a) required information to supplement the oral toxicity study and prove that not fasting the animals did not significantly alter the oral toxicity — OR

b) Submit new study(s) in oral toxicity particularly if the [redacted] formulation is to be used

3. If the [redacted] formulation is to be used, then a new eye irritation study must be submitted to decide if the test material is corrosive to the eye. This test must be extended to such a time that

NEIT INCIDENT INFORMATION IS NOT INCLUDED

it definitely decides the toxicity catagory.

Preferably the intervals of evaluation should be the ones suggested by the guidelines.

Committed 4. Dermal Toxicity study must be submitted using the new formulation(s)

Committed 5. Inhalation Toxicity study must be submitted using the new formulation(s)

Committed 6. A sensitization study must be submitted if the sensitization potential of of [redacted] is not established.

The Label can only be discussed upon the successful definition of the Toxicity profile of the new formulation.

INERT INGREDIENT INFORMATION IS NOT INCLUDED

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

Product Manager: (15) Reviewer: L. Markarian
MRID No.: none assigned Report Date: 2/12/91
Testing Facility: Merck, Sharp & Dohme Research Labs. Report No. 90-147-0
Author(s): Lea R. Gordon, Walter J. Bogdow, Mark E Cartwright
Species: Rat, Crl:CD (SD) BR
Age: 58 days old Observation Days (Post Exposure): (14) other ( )
Weight: ♂ 276-366g ♀ 201-248g
Source: Charles River Laboratories, Raleigh NC
Test Material: L-676, 863-304Y (MK-0936 [redacted] Formulation
Quality Assurance (40 CFR §160.12): not included

Conclusion:

1. LD_{50} (mg/kg): Males = 0.506 ml/kg (No confidence Limits); Females = 0.584 (0.465-0.729) ml/kg; Combined = 0.549 (0.481-0.624) ml/kg
2. The estimated LD_{50} is
3. Tox. Category: ____. Classification: Supplementary

Procedure (Deviations From §81-1): Unfasted rats were intubated with test material, as received, at five levels. A group of control animals were intubated with the vehicle only. Observations were frequent during the day of intubation and daily thereafter. Body weights were recorded at intubation and on days 1, 4, 8 + 11. Necropsy was performed on all animals. Animals were fasted prior to sacrifice.

Results:

Reported Mortality

DOSAGE (ml /kg)	(NUMBER KILLED/NUMBER TESTED) Males	Females	Combined
0.25	0/10	0/10	0/20
0.40	0/10	2/10	2/20
0.64	10/10	6/10	16/20
1.02	10/10	9/10	19/20
1.63	10/10	10/10	20/20
vehicle control 1.63	0/10	0/10	0/20

Symptomology & Gross Necropsy Findings:

All mortality occurred within three days after intubation. Symptoms of Neurotoxicity were expressed as Tremors, loss of righting reflex. Other symptoms of toxicity were decreased activity, red material around eyes and nose, vocalization, salivation and urine stains at all levels. Gasping was observed at levels higher than 4 ml/kg. Weight loss was noted at all levels between day 1 and day 4. Losses were somewhat recuperated at the end of the study, However, general gains in body weights in the test groups were lower than the gains in the test groups and there was a dose response relationship. One male at 4 ml/kg level still showed weight loss on day 11.
Necropsy of the animals, both dying spontaneously and sacrificed, revealed no product related gross pathology. Enlarged cervical lymph nodes & congested lungs + thymus gland were reported as commonly seen in the species in the general practice of the laboratory.

INERT INGREDIENT INFORMATION IS NOT INCLUDED

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

Product Manager: (15)
MRID No.: none assigned
Reviewer: L. Markarian
Report Date: 2/12/91
Testing Laboratory: Merck Sharp + Dohme Research Labs.
Report No. TT #90-2740
Author(s): L. Gordon, R. Eydelloth, W. Bagdon, & J. Shortridge
Species: Rabbit, New Zealand White
Sex: 5♂ & 5♀
Weight: 3.05 - 3.58 kg
Source: Hazleton Research Products, Inc. Denver, Pa
Dosage: 0.1ml
Test Material: L. 676.863 - 304Y (MK-0936 [redacted] formulation
Quality Assurance (40 CFR §160.12): Included

Summary:

Tox. Category: I
Classification: Core Minimum

Procedure (Deviation From §81-4): Test Material was instilled in the conjunctival sacs of the left eyes of rabbits. Six were observed unwashed and four after washing with 50ml of warm Tap water 20 seconds after instillation. It is not indicated if corneal observations were confirmed with fluorescein. Eyes were evaluated at 15 min, & 2hrs after instillation instead of 1hr. Evaluation of eyes was according to Draize.

Comments

Eyes need not be evaluated at 15 minutes. It is not clear how any observation can be made when grade 4 chemosis is present (@ 2hr interval) nor is it clear what is meant by mucoid discharge. Does it mean purulence or not must be clarified. If it is so obvious then the discharge could have been grade 2 - For all practical purposes irritation had subsided by day 7, as Grade 1 of any conjunctival irritation is considered non remarkable. Washed eyes not required.

Observations (number "positive"/number tested)

	Hour					Days						
	15 min	2 Hrs	24(1) Hrs	48(2) Hrs	72(3) Hrs	Day 4	DAY 7	DAY 8	DAY 9	DAY 10	DAY 11	DAY 14
UNWASHED: Cornea Opacity	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
Iris	4/6	1/6	3/6	2/6	1/6	1/6	0/6	0/6	0/6	0/6	0/6	0/6
Conjunctivae Redness	4/6	6/6	6/6	6/6	5/6	4/6	0/6	0/6	0/6	0/6	0/6	0/6
Chemosis	4/6	6/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
Discharge	6/6	6/6	3/6	2/6*	1/6*	1/6	0/6	0/6	0/6	0/6	0/6	0/6
CORNEAL ANESTHESIA	1/6	5/6	1/6	1/6	1/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
WASHED: Cornea Opacity	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
Iris	1/4	0/4	1/4	1/4	1/4	1/4	0/4	0/4	0/4	0/4	0/4	0/4
Conjunctivae Redness	3/4	4/4	4/4	4/4	4/4	4/4	0/4	0/4	0/4	0/4	0/4	0/4
Chemosis	2/4	3/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
Discharge	**	4/4	2/4*	0/4*	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
Corneal Anesthesia	0/6	1/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4

** discharge not evaluated at 15 min in washed eyes
* mucoid white discharge in 2 animals in washed group 1 animal in unwashed group Grade I

(10)

INERT INGREDIENT INFORMATION IS NOT INCLUDED

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

Product Manager: (15)
MRID No.: none Assigned
Reviewer: L. Markarian
Testing Laboratory: Merck, Sharp + Dohme Research Labs
Report Date: 2/12/91
Author(s): L. Gordon, R Eydelloth, W. Boyden + J. Shortridge
Report No. TT#90-2740
Species: Rabbit, New Zealand white
Sex: 5♂ + 5♀
Weight: 3.05 - 3.58
Source: Hazleton Research Products, Inc. Denver, Pa
Dosage: 0.1 ml
Test Material: L-930,780-000E (Vehicle for MK-0936 [redacted]
Quality Assurance (40 CFR §160.12): included

Summary:

Tox. Category: III Classification: core minimum

Procedure (Deviation From §81-4): Test Material was instilled in the conjunctival sacs of the left eyes of rabbits. Six were observed unwashed and four after washing with 50ml of warm Tap water 20 seconds after instillation. It is not indicated if corneal observations were confirmed with fluorescein. Eyes were evaluated at 15 min, and at 2 hrs after instillation instead of 1hr. Evaluations were according to Draize.

Comments: Eyes need not be evaluated at 15 minutes. It is not clear how any observation can be made when Grade 4 chemosis is present (at 2 hr) nor is it clear what is meant by mucoid discharge. Does it mean purulence? Must be clarified. If discharge is so obvious it possibly could have been grade 2. As Grade 1 irritation is any conjunctival observation is not remarkable all irritation is considered subsided by day 7. Washed eyes not required

Observations (number "positive"/number tested)

		Days											
		15 min	2 hrs	24 hrs (1)	48 hrs (2)	72 hrs (3)	Day 4	Day 7	Day 8	Day 9	Day 10	Day 11	Day 14
UNWASHED	Cornea Opacity	0/6	0/6	0/6	1/6	2/6	2/6	0/6	0/6	0/6	0/6	0/6	0/6
	Iris	3/6	0/6	4/6	2/6	1/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
	Conjunctivae Redness	6/6	6/6	6/6	6/6	4/6	4/6	0/6	0/6	0/6	0/6	0/6	0/6
	Chemosis	5/6	6/6	4/6	2/6	1/6	1/6	0/6	0/6	0/6	0/6	0/6	0/6
	Discharge	6/6	6/6	5/6*	4/6	1/6	1/6	0/6	0/6	0/6	0/6	0/6	0/6
	CORNEAL ANESTHESIA	0/6	2/6	0/6	3/6	2/6	2/6	0/6	0/6	0/6	0/6	0/6	0/6
WASHED	Cornea Opacity	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
	Iris	2/4	0/4	1/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
	Conjunctivae Redness	3/4	4/4	4/4	3/4	3/4	3/4	0/4	0/4	0/4	0/4	0/4	0/4
	chemosis	2/4	4/4	1/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
	Discharge	—	3/4	2/4	0/4**	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
	Corneal Anesthesia	0/4	1/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4

* no evaluation of discharge in washed eyes at 15 min
** white mucoid discharge 1 animal Grade 3 in unwashed Grade 1 in washed eyes

(11)

INERT INGREDIENT INFORMATION IS NOT INCLUDED

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

Product Manager: (15)
MRID No.: none assigned
Testing Laboratory: Merck, Sharp + Dohme Research Labs
Author(s): L. Gordon, W. Bagden, R. Eyedellotte, + J. Shortridge
Species: Rabbit, New Zealand white
Sex: 5 ♂ + 5 ♀
Source: Hazleton Research Products, Inc. Denver, Pa
Dosage: 0.1 ml
Test Material: L 676863-31DT [redacted] formulation) (MK-0936 [redacted] Formulation)
Quality Assurance (40 CFR §160.12):

Reviewer: L. Markarian
Report Date: 2/12/91
Report No. TT#90-2797

Summary:

Tox. Category: ____ Classification: Supplementary

Procedure (Deviation From §81-4): Test Material was instilled in the conjunctival sacs of the left eyes of rabbits. Six were observed unrinsed and four after washing with 50ml of warm tap water 20 seconds after instillation. Eyes were evaluated at 15 minutes and at 2 hrs after instillation. This was in place of 1hr. It is not indicated if corneal observations were confirmed with fluorescein. Evaluations were according to Draize

Comments Eyes need not be evaluated at 15 min. It is not clear how any evaluation can be made when Grade 4 Chemosis is present. (2hr interval). Washed eyes not required. When opacity is present at 14 days observations must be extended to 21 days to ascertain the permanence or the reversibility of the ocular lesion. Grade 1 opacity is considered remarkable, eyes were not normal at 14 days.

Observations (number "positive"/number tested)

	Hour					Days						
	15 min	2 Hrs	24 Hrs (1)	48 Hrs (2)	72 Hrs (3)	Day 5	Day 6	Day 7	Day 8	Day 9	Day 11	Day 13
UNWASHED: Cornea Opacity	0/6	0/6	0/6	0/6	1/6	3/6	3/6	3/6	3/6	3/6	1/6	1/6
UNWASHED: Iris	2/6	3/6	3/6	2/6	2/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
UNWASHED: Conjunctivae Redness	5/6	5/6	5/6	5/6	4/6	3/6	3/6	2/6	2/6	1/6	1/6	1/6
UNWASHED: Chemosis	5/6	5/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
UNWASHED: Discharge	6/6	6/6	6/6	1/6	3/6	1/6	1/6	1/6	1/6	1/6	1/6	1/6
UNWASHED: CORNEAL ANESTHESIA	1/6	5/6	4/6	4/6	4/6	2/6	2/6	2/6	2/6	2/6	1/6	1/6
WASHED: Cornea Opacity	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
WASHED: Iris	3/4	3/4	2/4	0/4	0/4	1/4	1/4	0/4	0/4	0/4	0/4	0/4
WASHED: Conjunctivae Redness	4/4	4/4	4/4	4/4	4/4	1/4	1/4	1/4	1/4	1/4	0/4	0/4
WASHED: chemosis	4/4	4/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
WASHED: Discharge	4/4	4/4	4/4	1/4	1/4	1/4	1/4	0/4	0/4	0/4	0/4	0/4
WASHED: Corneal Anesthesia	2/4	3/4	2/4	2/4	2/4	0/4	0/4	0/4	1/4	0/4	0/4	0/4

INERT INGREDIENT INFORMATION IS NOT INCLUDED

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

Product Manager: (15)
MRID No.: none Assigned
Reviewer: L. Markarian
Testing Laboratory: Merck, Sharp + Dohme Research Labs
Report Date: 2/12/91
Author(s): L. Gordon, W. Bagdon, R. Eydelloth, J. Shortliage
Report No. PT # 90-2797
Species: Rabbit, New Zealand White
Sex: 5♂ + 5♀
Weight: 2.15 - 2.63
Source: Harlan Research Products, Denver, Pa
Dosage: 0.1 ml
Test Material: L 676, 863-313A [redacted] formulation) (MK-0936 [redacted] Formulat
Quality Assurance (40 CFR §160.12):

Summary:

Tox. Category: II
Classification: Core minimum

Procedure (Deviation From §81-4): Test Material was instilled in the conjunctival sac of the left eyes of rabbits. Six were observed unwashed and four after washing with 500ml of warm tap water 20 seconds after instillation. Eyes were evaluated at 15 minutes and at 2 hrs after instillation instead of 1 hr. It is not indicated if corneal observations were confirmed with fluorescein. Evaluations were according to Draize.
Comments: Eyes need not be evaluated at 15 minutes. It is not clear how any evaluation can be made when Grade 4 chemosis is present (2 hr). Washed eyes are not required.

Observations (number "positive"/number tested)

	Hour	Days											
	15 min	2 hrs	24 hrs (1)	48 hrs (2)	72 hrs (3)	Day 5	Day 6	Day 7	Day 8	Day 9	Day 12	Day 13	[illegible]
UNWASHED													
Cornea Opacity	0/6	0/6	1/6	1/6	2/6	2/6	1/6	1/6 → ϕ	1/6 *	1/6 *	0/6	0/6	[illegible]
Iris	1/6	6/6	3/6	0/6	0/6	1/6	0/6	0/6	0/6	0/6	0/6	0/6	[illegible]
Conjunctivae Redness	6/6	6/6	6/6	6/6	4/6	2/6	1/6	1/6	1/6	0/6	0/6	0/6	[illegible]
Chemosis	5/6	6/6	3/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	[illegible]
Discharge	6/6	6/6	4/6	2/6	1/6	0/6	1/6	0/6	0/6	0/6	0/6	0/6	[illegible]
CORNEAL ANESTHESIA	0/6	6/6	5/6	4/6	3/6	1/6	1/6	0/6	0/6	0/6	0/6	0/6	[illegible]
WASHED													
Cornea Opacity	0/4	0/4	0/4	0/4	1/4	1/4	1/4	0/4	0/4	0/4	0/4	0/4	[illegible]
Iris	2/4	1/4	2/4	2/4	0/4	1/4	1/4	0/4	0/4	0/4	0/4	0/4	[illegible]
Conjunctivae Redness	4/4	4/4	4/4	4/4	3/4	2/4	1/4	1/4	1/4	0/4	0/4	0/4	[illegible]
Chemosis	4/4	4/4	1/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	[illegible]
Discharge	4/4	4/4	4/4	2/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	[illegible]
Corneal Anesthesia	0/4	4/4	3/4	3/4	1/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	[illegible]

* Vascularization of cornea 1/6 animals
ϕ mucosis 1/6 animals

INERT INGREDIENT INFORMATION IS NOT INCLUDED

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

Product Manager: (15) Reviewer: L. Markarian
MRID No.: none Assigned Report Date: _____
Testing Laboratory: Merck Sharp + Dohme Research Lab. Report No. TT#90-2741
Author(s): L. Gordon, W. Bagden, R. Eydelloth, J. Shortlidge
Species: Rabbit, New Zealand white, Hazleton Research Products, Denver, Pa.
Age: - 32 weeks old
Sex: 6♂ & 6♀
Weight: 3.03 - 3.88 kg
Dosage: 0.5 ml
Test Material: L-676,863-304Y (MK[redacted] formulation) & L-930,780-00E (Vehicle)
Quality Assurance (40 CFR §160.12): included

Summary:

The Primary Irritation Index =

Formulation	Intact	Abraded
	1.59	1.77
Vehicle	0.88	1.49

Toxicity Category: III

Classification: Core Minimum

Procedure (Deviations From §81-5): Animals were tested in two groups. One Group of 6 was treated with the complete formulation, and the second group of 6 was Treated with vehicle only. Each animal was treated at 4 sites, two intact and two abraded. Four 5x5cm sites were selected, covered with 2"x2" gauze pad held in place with adhesive tape and test material injected through the gauze on to the skin. The Trunks of the animals were wrapped in plastic occlusive dressing and collars were placed around the necks. At 24hrs the wrapping and collars were removed. The sites were washed with tap water. Evaluations were according to Draize at 24hrs, and on days 2, 3, 4, 7, 8, 9, 10, 11, 14, 15, 16, 17, 18, & 21. There was daily mortality check.

Results:

In both groups of animals the most irritation observed was Grade 2 erythema and grade 1 edema at intact or abraded sites. All remarkable irritation (Grade 2) subsided by day 7 in both groups. The over all reactions were slightly more pronounced in the test group, and abraded sites showed slightly higher grade of irritation. Scaling was observed in all groups at intact and abraded sites. The numbers of animals showing scaling were comparable in Test and Vehicle control groups. Fewer animals showed scaling among the intact sites. Grade 1 erythema persisted to Day 9 in two animals at the intact sites in the Test group. At abraded sites all were normal on day 7. In the Vehicle control group Grade 1 erythema persisted to day 8 at 1 intact and two abraded site.

Comments:

According to the guidelines Abraded sites are not required to be tested, applications should be made to a 6cm² area rather than a 5x5cm site. Exposure is to be for 4hrs and the results must be evaluated at 1, 24, 48, and 72 hrs. If Grade 2 or higher reaction is present at 72hrs then the observations are extended to 14 days. Primary irritation indices must be calculated using the results from the evaluations at 1, 24, 48 & 72 hrs.
The results do not point to the vehicle as the substance causing the irritation as stated in the report. The PI indices indicate the complete pesticide to be slightly more irritating than the vehicle.
"Scaling" needs to be defined. If there was no exfoliation it cannot be interpreted the desquamation. If it is indicative of initially stronger reactions at 24 hrs or later, then it must be explained.

Tox Chem No. 63 A B

Avermectin B_1

File Last Updated _____

Current Date 2/12/91

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX. Cat.	CORE Grade/ Doc. No.
Merck Sharpand Dohme Research Laboratories Hillsborough Road, Three Bridges New Jersey 08887	INERT INGREDIENT INFORMATION IS NOT INCLUDED				
Acute Oral Toxicity LD50 Study 90-147-0 8/28/90	L-676,863-304 Y (MK-0936 [redacted] Formulation	none assigned	LD_{50} ♂ 0.506 ml/kg (no confidence Limit) ♀ 0.584 (0.465-0.729) ml/kg combined 0.549 (0.481-0.629) ml/kg		Supplementary
Eye Irritation Test 90-2740	L-676,863-304 Y MK-0936 [redacted] Formulation	none assigned	Eye irritation cleared within 7 days	III	core minimum
	L-930,780-000E Vehicle for L-676,863-304Y	"	Eye irritation cleared within 7 days	III	core minimum
Eye Irritation Test 90-2797	L-676,863-304 Y MK-0936 [redacted] Formulation ([redacted] formulation)	none assigned			Supplementary
	L-676,863-313 A ([redacted] formulation)	none assigned	Eye irritant, opacity cleared within 14 days	II	core minimum
Dermal Irritation Test 90-2741	L-676,863-304 Y MK-0936 [redacted] Formulation	none assigned	PII intact 1.59 Abraded 1.77	III	core minimum
	L-930,780-000E	none	PII intact 0.88 Abraded 1.49	III	core minimum