7-30-85

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

004593

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Acute Studies; Waiver Requests; Preliminary Report Indicating Dose-Related Carcinogens in Female Mice

FROM: Thomas Edwards, Pharmacologist W Thomas Edwards 7-29-85
Hazard Evaluation Division (TS-769)

TO: Registration Division (TS-767)

THRU: Clint Skinner, Section Chief
Toxicology Branch, HED (TS-769) Clint Skinner 7-30-85

Chemical: EL-107

Caswell No.: 419F

EPA Registration No.: 1471-EUP-TN, 5G3216

Accession Nos.: 25769, 257774

Requested Actions: Review and Comment

Note that other studies needed to support the EUP and temporary tolerance request are under review separately. Reviews of studies are attached. Results of the acute studies were as follows:

Acute oral LD50, rat: more than 5000 mg EL-107 DF (75%) per kg bw. Acute oral toxicity category: IV.

Acute dermal LD50, rabbit: more than 5000 mg EL-107 DF (75%) per kg bw. Acute dermal toxicity category: III. Primary irritation category: III.

Primary eye irritation category (EL-107 DF 75%): III.

Acute inhalation LC50 (4 hours, EL-107, technical): 2.55 ± 0.603 (SD) mg/L (HDT). Acute inhalation toxicity category: III.

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Dermal sensitization (EL-107, technical): not sensitizing.

Dermal sensitization (Balan DF): not sensitizing.

The requested waiver of the dermal sensitization study for the formulated product EL-107 DF (75%) was supported by a study using EL-107, technical and a study for Balan DF which has the same "inerts" as EL-107 DF (75%), except [redacted] Both EL-107, technical and Balan DF were found to be not sensitizing. It is agreed that the acute sensitization study for EL-107 DF (75%) is not needed.

As requested, the acute inhalation study for EL-107 DF (75%) can be waived, but only if category III labeling is used.

An apparently dose-related increase in incidence of hepatocellular carcinomas in female mice was reported. When the final report from the registrant is received, a statistical analysis will be made for both species, mouse and rat, to evaluate associated hazard.

Data from the registrant will be referred to our statistician for evaluation of the dose-response relationship for indicated data sets, i.e., the dependent variables (such as tumor types or grouping) adjusting for, or accounting for the effects of conditioning factors and covariates including time to diagnosis or death. His results will be used to evaluate the biological implications and aid in determining the regulatory options arising from the findings.

Reporting of all principal tumor types for statistical analysis is recommended, for two reasons. It is frequently desirable to evaluate the total number of tumor-bearing animals as well as the subtotal with malignant tumors. Secondly, it is necessary to know the total number of animals with each tumor type to estimate the probability of observing statistically significant finding of any type of tumor and particularly for the tumor type of interest given the data in the study. Such analysis could minimize the possiblity of recommending action arising from false positive. Principal types of tumors in a particular study may include:

1) Any type of tumor which has a high incidence in all groups, including controls.

2) Tumor types with higher apparent incidence in treated group(s) compared to controls.

3) Tumor types which support a positive dose response trend.

4) Rare tumor types observed in the test groups.

To support the final tables needed by the statistician, the following should be included along with other pertinent feeding study results. Three types of data for pathology: the summary incidence table per group - per sex for each organ; the individual tabulation of lesions per organ and thirdly individual pathology sheets containing the gross findings and other data reported (date of death, type of death, applicable microscopic findings). The chemical data needed should be available on tables showing findings for the individual animals examined at specific times. Weight gain and food consumption should also be available on summary tables for each group and sex and for individual animals.

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TOXICOLOGY BRANCH
DATA REVIEW

Study Type: Acute Oral Toxicity, Rat

Accession Number: 257774

MRID Number:

Sponsor: Eli Lilly, No. R-0-01-85

Contracting Lab:

Date: January 18, 1985

Test Material: EL-107 DF (75%) (FN-3133)

Protocol: See attached Materials and Methods.

Results:

5000 mg/kg was the only dose level.

There were no deaths.

Signs of toxicity were hypoactivity and leg weakness. Both males and females had what appeared to be test compound in feces. Also, males had diarrhea. All animals appeared normal by 2 days after dosing.

Conclusions:

Acute Oral LD_{50}: more than 5000 mg/kg

Acute Oral Toxicity Category: IV

Core Classification:

Guideline

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____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

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TOXICOLOGY BRANCH
DATA REVIEW

Study Type: Acute Dermal Toxicity and Primary Dermal Irritation, Rabbit

Accession Number: 257774

MRID Number:

Sponsor: Eli Lilly, No. E-D-196-84

Contracting Lab:

Date: December 19, 1984

Test Material: EL-107 DF (75%) (FN-3133)

Protocol: See attached Materials and Methods.

Results:

There were no deaths during the observation period (14 days).

No overt signs of systemic toxicity or other treatment-related effects were observed other than moderate erythema and slight edema at treatment sites which developed within 24 hours after treatment and cleared within 5 days.

Conclusions:

Acute Dermal LD_{50}: more than 5000 mg/kg

Acute Dermal Toxicity Category: III

(The study is not adequate for a category indicating less toxicity).

Primary Irritation Category: III

Core Classification:

Minimum

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TOXICOLOGY BRANCH
DATA REVIEW

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Study Type: Primary Eye Irritation, Rabbit

Accession Number: 257774

MRID Number:

Sponsor: Eli Lilly, No. B-E-206-84

Contracting Lab:

Date: December 17, 1984

Test Material: EL-107 DF (75%) (FN-3133)

Protocol: See attached Materials and Methods

Results:

Corneal dullness, slight iritis, moderate conjunctival hyperemia, and slight to moderate conjuntival chemosis developed in treated eyes within one hour after exposure. Treated eyes in two of six animals gave a positive response to sodium fluorescein dye instilled 24 hours after treatment. Iridal irritation cleared in all treated eyes within 48 hours after treatment. All fluorescein results were negative 72 hours after treatment. Conjunctivitis cleared in five of six animals within 7 days and in the sixth within 14 days.

Conclusions:

Eye Irritation Category: III

Core Classification:

Guideline

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TOXICOLOGY BRANCH
DATA REVIEW

Study Type: Acute Inhalation Toxicity (4-hours), rat

Accession Number: 257774

MRID Number:

Sponsor: Eli Lilly No. R-H-70-84

Contracting Lab:

Date: October 29, 1984

Test Material: EL-107, Technical

Protocol: See Attached Materials and Methods.

Appendix E presents Shell's rationale for using EL-107 technical material instead of EL-107 DF in this acute inhalation study.

It is agreed that this substitution is acceptable.

Results:

The nominal concentration was 12.83 mg/L. The gravimetric exposure concentration was 2.55 ± 0.603 (SD) (range was 1.55 to 3.47 mg/L).

The mass median equivalent aerodynamic diameter was determined to be 40.49 µm with a geometric standard deviation of 4.28. The particle size distribution pattern is shown in Figure 2 of Appendix E.

All animals appeared normal throughout the study with the exception that five female rats displayed poor grooming in day 1.

There were no deaths and no compound-related lesions were found.

Conclusions:

Acute inhalation toxicity (4 hours): 2.55 ± 0.603 (SD) mg/L (HDT).

Acute inhalation toxicity category: III

Core Classification:

Minimum

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____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

✓ FIFRA registration data.

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TOXICOLOGY BRANCH
DATA REVIEW

Study Type: Dermal sensitization, guinea pig

Accession Number: 257774

MRID Number:

Sponsor: Eli Lilly, No. G00183

Contracting Lab:

Date: December 1983

Test Material: EL-107, Technical and a suspension concentrate formulation (FN-7033) containing 50% EL-107.

Protocol:

Female guinea pigs of the Hartman strain were used.

Treatment groups and study duration were as follows.

"Group I: Induction and Challenge: 0.1% dinitrochlorobenzene (DNCB) in 70% ethanol

Group II: Challenge Control: 0.1% DNCB in 70% ethanol

Group III: Induction and Challenge: EL-107, technical material, at a concentration of 25% in 95% ethanol

Group IV: Challenge Control: EL-107, technical material, at a concentration of 25% in 95% ethanol

Group V: Induction and Challenge: A 1:1 aqueous dilution of the suspension concentrate formulation

Group VI: Challenge Control: A 1:1 aqueous dilution of the suspension concentrate formulation

"There were 12 animals in each induction and challenge group; each challenge control group contained 6 animals. The duration of the study was 24 days."

The suspension concentration formulation 50% contained EL-107. It was not the same formulation as EL-107 DF (75%).

"Animals were induced three times a week for 2 consecutive weeks in induction and challenge test groups (Groups 1, 3, and 5). Guinea pigs were prepared for treatment by clipping the hair in the nuchal area with Oster® clippers. Exposed skin was swabbed with acetone to remove extraneous lipid material that might inhibit percutaneous absorption. A dose of 0.2 ml of the test material was applied to the nuchal area of each animal. The application site was occluded with a 1 1/2 inch square patch (Band-Aid®) held in place with adhesive tape which was wrapped around the torso of the animal. The bandage was removed after 6 hours."

"Guinea pigs assigned to challenge control groups (Groups 2, 4, and 6) were left untreated during the induction period."

"Ten days following the last induction exposure, the challenge dose was administered to all test animals including the challenge controls. A previously untreated area in the center of the back of each animal was prepared for treatment by clipping the hair and swabbing the exposed skin with acetone. Each application site was treated and occluded for 6 hours as described for induction."

"During the induction and challenge phases of the study, treated areas were graded for dermal response 24 hours after each application of EL-107 according to the method outlined in Appendix D. Similar observations were conducted 24, 48, and 72 hours following challenge."

"Body weights were recorded at test initiation and weekly during the test period."

Results:

There was no sign of sensitization or dermal irritation in any of the animals challenged with either EL-107 technical or the suspension concentrate formulation (50% formulation).

The positive control gave positive results.

Conclusion:

Dermal sensitization was not found.

Core Classification: 25

Minimum

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TOXICOLOGY BRANCH
DATA REVIEW

tudy Type: Dermal sensitization, guinea pig

ccession Number: 257774

RID Number:

ponsor: Eli Lilly, No. G01184

ontracting Lab:

ate: September 1984

est Material: Balan DF (FN-3045) (60% benefin)

rotocol:

Female albino guinea pigs of the Hartley strain were used.

Four treatment groups were identified as follows.

"Group I: Induction and Challenge: Balan DF at doses of 50 mg, tested as triturated powder.

Group II: Challenge Control: Balan DF at doses of 50 mg, tested at triturated powder.

Group V: Induction and Challenge: 0.1% dinitrochlorobenzene (DNCB) in 70% ethanol at doses of 0.2 ml.

Group VI: Challenge Control: 0.1% DNCB in 70% ethanol at doses of 0.2 ml."

"There were 12 animals in each induction and challenge group; ach challenge control group contained 6 animals. The duration f the study was 24 days."

"In the induction and challenge test groups (I and V), animals were treated three times a week for 2 consecutive weeks (induction) then rested for 10 days prior to the challenge application. The challenge control groups (II and VI) were left untreated during induction but received the challenge treatment."

"The guinea pigs were prepared for treatment by clipping the hair in the nuchal area with Oster® clippers and swabbing the exposed skin with acetone. The acetone wash was to remove extraneous lipid material that might inhibit percutaneous absorption. Each induction treatment was to the nuchal area, which was occluded with a 1 1/2 inch square patch (Band-Aid®) held in place with adhesive tape for 6 hours. At the end of 6 hours, the patch was removed and the excess material was brushed off the treatment site."

"The challenge dose was administered to a previously untreated area in the center of the back of each animal, which was prepared for treatment by clipping the hair and swabbing the exposed skin with acetone. The challenge application site was treated, occluded for 6 hours, and brushed off excess material as described for induction."

"Twenty-four hours after each induction exposure and after the challenge application, treated areas were graded for dermal response according to the method outlined in Appendix D. Observations were also conducted 48 and 72 hours following challenge."

"Body weights were recorded at test initiation and weekly during the test period."

Results:

As shown in tables 1 and 3, Balan DF was a slight irritant but not a contact sensitizer.

The positive control gave positive results.

Conclusion:

Dermal sensitization was not found.

Core classification:

Minimum

TABLE 1.

DERMAL RESPONSE* SCORES FOR GUINEA PIGS 24 HOURS AFTER EACH INDUCTION APPLICATION OF BALAN® DF. STUDY G01184.

Animal Number	1		2		3		4		5		6	
	Erythema	Edema	Erythema	Edema	Erythema	Edema	Erythema	Edema	Erythema	Edema	Erythema	Edema
051	0	0	0	0	0	0	0	0	0	0	0	0
052	0	0	0	0	0	0	0	0	0	0	1	0
053	0	0	0	0	0	0	0	0	0	0	0	0
054	0	0	0	0	0	0	0	0	0	0	3	1
055	0	0	0	0	0	0	0	0	0	0	1	1
056	0	0	0	0	0	0	0	0	0	0	0	0
057	0	0	0	0	0	0	0	0	0	0	1	0
058	0	0	0	0	0	0	0	0	0	0	0	0
059	0	0	0	0	0	0	0	0	0	0	0	0
060	0	0	0	0	0	0	0	0	0	0	0	0
061	0	0	0	0	0	0	0	0	0	0	0	0
062	0	0	0	0	0	0	0	0	0	0	0	0
063	Not Treated											
064	Not Treated											
065	Not Treated											
066	Not Treated											
067	Not Treated											
068	Not Treated											

*Based on the scoring system described in Appendix D.

TABLE 3.
DERMAL RESPONSE* SCORES FOR GUINEA PIGS CHALLENGED WITH BALAN® DF. STUDY G01184.

Animal Number	Dose of Balan® DF		Response to Challenge: Hours After Challenge					
			24 Hours		48 Hours		72 Hours	
	Induction	Challenge	Erythema	Edema	Erythema	Edema	Erythema	Edema
051	50 mg	50 mg	0	0	0	0	0	0
052	50 mg	50 mg	0	0	0	0	0	0
053	50 mg	50 mg	0	0	1	0	1	0
054	50 mg	50 mg	1	0	2	0	2	0
055	50 mg	50 mg	0	0	2	1	2	1
056	50 mg	50 mg	2	0	0	0	0	0
057	50 mg	50 mg	0	0	2	1	2	1
058	50 mg	50 mg	1	0	0	0	0	0
059	50 mg	50 mg	0	0	1	0	1	0
060	50 mg	50 mg	0	0	0	0	0	0
061	50 mg	50 mg	0	0	1	0	1	1
062	50 mg	50 mg	0	0	1	0	1	0
063	Not Treated	50 mg	0	0	0	0	0	0
064	Not Treated	50 mg	0	0	2	0	0	0
065	Not Treated	50 mg	0	0	0	0	1	0
066	Not Treated	50 mg	0	0	0	0	0	0
067	Not Treated	50 mg	0	0	0	0	0	0
068	Not Treated	50 mg	0	0	1	0	1	0

*Based on the scoring system described in Appendix D.