7-24-84

Caswell No(s).: 419F

To: Taylor/Howell 004034

Registration No(s).:

Pesticide Petition No(s).: 1471-EUP-IL

Chemical(s): EL-107

Requested Action(s): additional studies

Recommendation: Sensitization Study is accepted. 21-day dermal toxicity study is inadequate. [redacted], See attached reviews and communications.

Inert(s) cleared 180.1001: N/A, See comments

% of ADI occupied: Existing: Resulting:

Resulting % increase in TMRC:

Data considered in setting the ADI:

Attached (?): ADI printout: YES/NO ; TOX "one-liner": YES/NO ; DER: YES/NO

Existing regulatory actions against registration:

RPAR status:

New Data: See attached reviews

Data gaps:

INERT INGREDIENT INFORMATION IS NOT INCLUDED

Comments: Refer to previous communications. [redacted] have not been identified.

6-29-84

Reviewer: W Kames Edwards Date: 7-24-84 WSD

Williamson Butts 7-23-84

ISOXABEN 125851

Page 2 is not included in this copy.

Pages _____ through _____ are not included.

The material not included contains the following type of information:

X 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.

____ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

28 Appendix C

Legal

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cc: Mr. J. F. B

FORMULATION DATA SHEET

Product Title: EL107 5050

Pesticide Type: HERBICIDE Product Form: SC

Date Submitted: 12-21-82 Project No.: T4A

FM No.: FM7030 Lot No.: X35660

Country of Interest: UK

Special Instructions: SAME FORMULATION AS SAF 437 FOR ACUTE TOX STUDY. THE TECHNICAL CONTAINS [redacted]

INERT INGREDIENT INFORMATION IS NOT INCLUDED

Formula:

INGREDIENT	% ACTIVITY	CA NO.	% S
EL 107	78.4		54
[redacted]			

[redacted]

BEST AVAILABLE COPY

Flashpoint: NA

Flammable Ingredient:

Density: 1.123G/ML@25C

Storage Restrictions:

AM:

Miscellaneous Information: LOT OF EL107 TECHNICAL USED AR-266-110

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TOXICOLOGY BRANCH
DATA REVIEW

Study Type: Dermal Sensitization, Guinea pig

Accession Number: 252915

MRID Number:

Sponsor: Eli Lilly and Co.

Contracting Lab: Eli Lilly Res. Labs., no. G00183

Date: December 1983.

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

Protocol:

"EL-107 and a suspension concentrate formulation (FN-7033) containing 50% EL-107 were evaluated for sensitization in female albino guinea pigs according to a modified Buehler topical patch method."

"Treatment Groups and Study Duration: The six treatment groups wer identified 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

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

Test Article

"EL-107 was tested at a concentration of 25% in a 95% ethanol in water solution."

The suspension concentrate used in this study was identified as formulation FN-7033, sample lot X-38660, and was tested as a 1:1 aqueous dilution. As a positive control, dinitrochlorobenzene (DNCB), lot 33152-A (ICN Pharmaceuticals), was adminsitered at a concentration of 0.1% w/v in a 70% ethanolic solution."

"Test Article Administration: The study was conducted in two phases: induction and challenge. Animals were induced three times a week for two 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 six hours.

Guinea pigs assigned to challenge control groups (Groups 2, 4, and 6) 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 six hours as described for induction.

Observations: During the induction and challenge phases of the study, treated areas were graded for dermal response 24 hours after each application of EL-107. Similar observations were conducted 24, 48, and 72 hours following challenge.

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

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Results:

"Survival

All animals survived.

Response to Challenge

The dermal response to challenge with either EL-107 or the suspension concentrate formulation containing 50% EL-107 was negative. DNCB produced a positive sensitization response.

Body Weights

All animals gained weight during the study."

Conclusions:

Under the conditions of this test (sensitization dosing by dermal application), there was no indication of contact sensitization or dermal irritation in guinea pigs exposed topically to technical EL-107 or the suspension concentrate (FN-7033) containing EL-107.

The positive control gave positive results

Core classification: Minimum

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TOXICOLOGY BRANCH
DATA REVIEW

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Study Type: 21 Day Dermal Toxicity, Rabbit

Accession Number: 252915

MRID Number:

Sponsor: Eli Lilly and Co.

Contracting Lab: Eli Lilly Res. Labs., no. B01783

Date: December 1983.

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

Procedure:

"Treatment Groups and Study Duration: The test rabbits were randomly distributed among one untreated control group and four treatment groups, each of which contained five males and five females." The groups were as follows:

0) Untreated Control (water rinse only)

1) 1055 mg EL-107/kg body weight (equivalent to 1000 mg active technical EL-107/kg)

2) 500 mg formulation/kg body weight

3) 1000 mg formulation/kg body weight

4) 1000 mg formulation/kg body weight (reversibility group received treatment for three weeks followed by a two week withdrawal period)

"All animals were treated daily for 21 consecutive days and then necropsied, except rabbits in the reversibility group, which were held an additional 14 days without further treatment in order to assess delayed systemic toxicity and reversibility of observed effects. The overall study duration was 35 days."

"Test Article Administration: The skin on the back of each animal was prepared for treatment by removing the fur with Oster clippers. The treatment site was reclipped a minimum of twice each week during the study.

Each dose of technical material was weighed on a Sartorius balance to the nearest 0.01 g. Technical test material was held in place on the back of each rabbit with a damp gauze pad. The suspension concentrate formulation was measured by volume to the nearest 0.1 ml and applied with a syringe to a gauze pad. Following application of either test material to

a gauze pad, the torso of each rabbit was wrapped with an elastic bandage, which was held in place with strips of tape. Dressings were removed after six hours and the application sites were rinsed with tap water and dried with a towel. All rabbits were provided with collars to discourage ingestion of the test material."

"Survival, Clinical Observations, and Dermal Irritation: Twice each day all cages were inspected for dead or moribund animals. Each rabbit was removed from its cage once a day for treatment application and carefully examined for changes in behavior or appearance. Dermal irritation was graded daily using an eight point scale for erythema and edema according to the method of Draize.

Body Weight and Food Consumption: Rabbits were weighed once each week and doses were adjusted to correspond to changes in body weight. Food consumption was measured daily.

Hematology: Hematologic evaluations were conducted on each rabbit prior to study initiation, at termination of treatment, and with the reversibility group, two weeks after the last exposure. Blood samples were drawn from the medial artery of the ear. Hematologic parameters included: hemoglobin (HGB), mean corpuscular volume (MCV), erythrocyte morphology, erythrocyte count, packed cell volume (PCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC). Hematology methodology is contained in Appendix F.

Clinical Chemistry: Blood samples for clinical chemistry evaluations were collected concurrently with those for hematology. Serum samples were analyzed for glucose (GLU), blood urea nitrogen (BUN), creatinine (CREAT), total bilirubin (TB), alkaline phosphatase (AP), and alanine transaminase (ALT)."

"Organ Weights: At necropsy, the liver, kidney, heart, thyroids, adrenals, ovaries, testes, and spleen were trimmed and weighed. Organ weight relative to 100 g body weight was calculated for all animals.

Pathology: All animals were necropsied. The necropsy was a systematic gross examination of each animal's general physical condition, body orifices, external and internal organs and tissues. All necropsies were performed by pathologists whose findings were recorded. The following organs and tissues for histopathologic examination were collected and immersed in a fixative: kidney, liver, heart, lung, spleen, thymus, lymph node, salivary gland, pancreas, stomach, duodenum, jejunum, ileum, colon, ovary, uterus, adrenal, thyroid, testis, prostate, skin, mammary gland, skeletal muscle, urinary bladder, bone marrow, eye, cerebrum, cerebellum, brain stem, application site, gallbladder, gross lesions, and skin.

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Three sections of skin were collected: abdominal skin, treated skin from the back, and untreated skin from the back.

Histologic preparations of the tissue specimens collected at necropsy were examined microscopically by a certified veterinary pathologist with experience in evaluating laboratory animal tissues. The findings were recorded and tabulated. A summary of the important pathologic alterations was prepared.

Statistics: The statistical method described by Dunnett was used in the analysis of differences (at each time point) between control and treated group means for parameters for which data are generally distributed normally (body weight, weight gain, hematology, clinical chemistry, and organ weight data). The homogeneity of variances was tested by the method of Bartlett.[5] All references to statistical significance in the report represent a "p" value ≤ 0.05."

Results:

"Clinical Observations

There were no overt signs of systemic toxicity related to the administration of EL-107 or a suspension concentrate formulation containing 50% EL-107. No treatment related changes or abnormalities occurred between the pretest ophthalmic and physical examinations and those conducted at termination of the study.

Body Weight

Terminal mean body weights were similar for control and treated animals.

Food Consumption

There were no treatment-related effects.

Dermal Irritation

The only evidence of dermal irritation in any treatment group was transient irritation which occurred in four of 20 animals exposed to 1000 mg formulation/kg body weight during the first week of treatment.

Hematology

There were no toxicologically important effects on erythrocyte and leukocyte counts, hemoglobin, packed cell volume, leukocyte differential count and erythrocyte morphology conducted pretest, at study termination, and 14 days after termination of treatment for the reversibility group.

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Clinical Chemistry

There were no toxicologically significant effects on glucose, urea nitrogen, creatinine, total bilirubin, alanine transaminase, or alkaline phosphatase determinations conducted pretest, at study termination, and 14 days after termination of treatment for the reversibility group."

"Organ Weights

Absolute and relative (per 100 g body weight) liver, kidney, heart, adrenal, ovary, testis, and spleen weights were not affected by technical EL-107 or the suspension concentrate containing 50% EL-107."

Increases in relative thyroid weights are shown in the following table which was adapted from information furnished.

TERMINAL BODY WEIGHT AND ORGAN WEIGHTS RELATIVE TO BODY WEIGHT

Treatment groups		Males		Females	
		Body Weights KG	Thyroids Para Thyroids MG per 100 G Body Weight	Body Weight KG	Thyroids Para Thyroids MG per 100 G Body Weight
Controls	MN	3.1	5.93	3.3	6.47
	SD	0.28	0.873	0.25	2.017
	SE	0.12	0.390	0.11	0.902
	OBS	5	5	5	5
1	MN	3.2	7.58	3.2	7.99
	SD	0.27	2.525	0.37	0.717
	SE	0.12	1.129	0.17	0.320
	OBS	5	5	5	5
2	MN	3.4	7.12	3.3	7.83
	SD	0.50	1.400	0.23	2.128
	SE	0.22	0.626	0.10	0.952
	OBS	5	5	5	5
3	MN	3.2	9.10	3.2	11.47**
	SD	0.43	4.143	0.50	2.410
	SE	0.19	1.853	0.23	1.078
	OBS	5	5	5	5
4	MN	3.1	5.59	3.4	6.35
	SD	0.19	0.816	0.51	1.482
	SE	0.09	0.365	0.23	0.663
	OBS	5	5	5	5

Group 4 had been allowed two weeks to recover.

"Pathology

There was no morphologic evidence of systemic toxicity or dermal irritation in rabbits following the dermal application of technical EL-107, or a suspension concentrate formulation containing 50% EL-107."

CONCLUSIONS:

Very slight dermal irritation in four of 20 animals exposed to 1000 mg formulation/kg body weight was observed.

The systemic effect of concern was increase in relative weights of the thyroid glands. Although there was much variation in thyroid plus parathyroid relative weights within groups, there was an increase in relative thyroid weight apparent in all treated groups except in the group which was allowed a two week recovery period.

LEL(technical EL-107): <1055 mg/kg bw

EL(formulation FN-7033): < 500mg/kg bw

This study was well performed but if considered alone is inadequate for regulatory purposes because a NOEL was not determined.

Core Classification:

Minimum