UNDATED

Toxicology Branch/HED Review

Casuell No(s).: 419 F

To: Taylor / Yowell 003773

Registration No(s).:

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

Chemical(s): EL-107

Requested Action(s): Review for EUP, Interim report.

Recommendation: This report is acceptable for EUP. see comments below

Inert(s) cleared 180.1001:

% 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:

Data gaps:

Comments: This reproduction studys indicate that a teratology stud. is needed for registration.

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Reviewer: Thomas Edwards Date:

Section Head: William Burnett Jr. Branch Chief.

003773

TOXICOLOGY BRANCH
DATA REVEIW

Study Type: 3- Generation reproduction study (interim report) RAT

Accession: 251939

MRID Number:

Sponsor: Eli Lilly and Co.

Contracting Lab: Lilly Research Lab. Nos, R 15382, R 03783, and R 14183

Date: December, 1983

Test Material: EL-107, Technical

"EL-107 is a mixture of isomers consisting primarily of Lilly compound 121607, N-[3-(1-ethyl-1-methylpropyl)-5-isoxazolyl]-2,6-dimethoxybenzamide; [redacted] Lot H02-2G6-118 (dried) and lot Z10025 of technical EL-107, prepared by Lilly Research Laboratories, Indianapolis, were used for this study. The initial potency of lot H02-2G6-118 was 93.7% [redacted] This lot of technical EL-107 was used for diet preparations at study initiation and prior to March 14, 1983. Because of an oversight, reassay values for potency of lot H02-2G6-118 (dried) are not currently available. Beginning on March 14, 1983, lot Z10025 was used for diet preparations. The potency of lot Z10025 was 95.5% [redacted] Lot Z10025 will be reassayed for potency in conjunction with concurrent two-year rodent studies with EL-107."

Protocol:

"EL-107 was administered to two parental generations of rats and will be administered to a third generation as a component of the diet at levels of 0, 0.5, 0.25, or 1.25% (equivalent to 0, 500, 2500, and 12500 ppm in the diet, respectively).

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

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"F_0 Generation (Study R15382): Weanling males and females (25/sex/group) were maintained on treatment diets for a growth period of 70 days and throughout two breeding trials. Immediately following the growth period, at ca 15 weeks of age, animals from corresponding treatment groups were mated. The females were allowed to deliver and rear their f_{1a} progeny through postpartum day 21 and weaning. Twenty-five f_{1a} weanling pups/sex/group were selected to become F_1 parents. Of the remaining weanlings, five/sex/group were given external and internal examinations and tissues were collected for histopathologic evaluation. At ca 25 weeks of age, the F_0 animals from corresponding treatment groups were again mated. All females were allowed to deliver and rear their f_{1b} progeny through postpartum day 21. At ca 33 weeks of age, the surviving F_0 parental animals were killed, given gross examinations, and reproductive tissues and livers were collected for histopathologic evaluation in addition, liver weights were obtained."

"F_1Generation (Study R03783): Weanling males and females were maintained on treatment diets for a growth period of 70 days and throughout two breeding trials. They will be continued on these diets until termination of the F_1 generation. Immediately following the growth period, at ca 15 weeks of age, the rats from corresponding treatment groups were mated. The females were allowed to deliver and rear their f_{2a} progeny through postpartum day 21 and weaning. Five f_{2a} weanlings/sex/treatment group were given external and internal examination and tissues were collected for histopathologic evalution. At ca 24 weeks of age, the F_1 rats from corresponding treatment groups were agian mated. All females were allowed to deliver and rear their f_{2b} progeny through postpartum day 21 and weaning. Twenty-five f_{2b} weanling pup/sex/treatment group were selected to become F_2 generation parents. Two additional groups of weanlings were retained and will be maintained with initial test groups. One group consisted of progeny of the high dose group with suspected eye defects and additional male weanlings of the same group (Appendices A.12 and A.14). The second group consisted of 20 weanlings of the control group (Appenddix A.14)). All f_{2b} weanlings were examined for ocular abnormalities (Appendix A.13).

Weanlings not selected to become F_2 generation parents killed and given external and internal examinations. At ca 35 weeks of age, the F_1 rats from corresponding treatment groups will be mated a third time. All pregnant F_1 females will be killed on gestation day 20 and given a complete teratologic evaluation. At termination, F_1 males and females will be given gross examinations, and reproductive tissues and livers will be collected for histopathologic evaluation. In addition, liver weights will be obtained."

"F_2 Generation (Study R14183): Weanling males and females will be maintained on treatment diets for a growth period of 70 days and until termination of the study. Immediately following the growth period, at ca 16 weeks of age, the rats from corresponding treatment groups will be mated. All pregnant F_2 females will be killed on gestation day 20 and given a complete teratologic evaluation. At termination, F_2 males and females will be given gross examinations, and reproductive tissues and livers will be collected for histopathologic evalution. In addition, liver weights will be obtained."

Physical Signs: During the growth periods, the animals were examined daily to determine their general condition. In addition, at least once each week a close observation was made of each animals noting muscle tone, pelage, eyes, teeth, secretions, and excretions. During the breeding trials, the females were closely observed near their time of parturition. Conditions occurring in the offspring were noted at the times of weighing."

"Pathology: The animals were necropsied following death. The necropsy was systematic gross examination of each animal's general physical condition, body orifices, and external and internal organs and tissues.

The following organs and tissues were collected for histopathologic examination from representative f_{1a} and f_{2a} weanlings and immersed in a fixative: kidney, liver, heart, lung, spleen, thymus, lymph node, salivary gland, pancreas, stomach, duodenum, jejunum, ileum, colon, ovary, uterus, adrenal, thyriod, testis, prostate, skin, mammary gland, skeletal muscle, and urinary bladder.

The following organs and tissues were collected for histopathologic examination from adult F_0 animals and immersed in a fixative: liver, ovary, uterus, testis, prostate, epididymis, seminal vesicle, mammary gland (females), and vagina.

Both eyes were collected from designated f_{2b} progeny and immersed in a fixative.

Histologic preparations of the tissues specimens collected at necropsy were examined microscopically by a veterinary pathologist with experience in evaluating laboratory animals tissues. The findings were recorded and tabulated. A summary of the important pathologic alteration was prepared. Particular attention was directed to the interpretation of treatment-related lesions."

Since no treatment-related [histopathologic] lesions were found, only tissues from the control and high-dose groups were examined microscopically."

Results:

"This interim report includes growth phase measurements for the F_0 and F_1 parental animals; reproduction measurements for two breeding trials in both the F_0 and F_1 generations including progeny observations and examinations for the f_{1a}, f_{1b}, f_{2a}, and f_{2b} litters; ophthalmic examinations of the f_{2b} progeny; findings from gross examinations of F_0 parental animals, and f_{1a}, f_{2a} and f_{2a} progeny; and histopathologic evaluations of tissues collected from F_0 parental animals and f_{1a} progeny. These data represent the majority of findings that would be reported for a two-generation reproduction study in rats."

There were no apparent effects on mating performance or fertility.

Body weight effects were observed in the 0.25 and 1.25 ppm groups. "The mean body weights of EL-107 treatment F_0 parental male and female rats and F_1 parental male rats did not differ significantly from the control values during the respective growth periods. However, growth (mean body weight and body weight gain) of F_1 parental females given diets containing 1.25% EL-107 was significantly depresses during

this period. There were no significant differences in mean body weights of either F_0 or F_1 parental males during the respective breeding trials. However, body weight depression was observed in pregnant and in lactating females given diets containing 0.25 or 1.25% EL-107. During the F_0 generation, significant body weight depression was observed only in females of the 1.25% dose group, and only during the second breeding trial. During the F_1 generation, body weights of females of the 0.25 and 1.25% groups were affected during both breeding trials. A significant depression in mean weight gain during gestation was observed in females of 1.25% group in all four delivery trials. This effect was limited to the 1.25% group. Body weights and weight gain in females of the 0.05% group were not affected by exposure to EL-107."

At the 1.25 ppm level there were depressed milk production and litter size and increased incidence of anomalies including exencephally and microphthalia.

Conclusions:

Parental effects:

NOEL: 0.05 ppm
LEL: 0.25 ppm (depressed females body weights)

Fetal toxicity (perhaps including Teratology)

NOEL: 0.25 ppm
LEL: 1.25 ppm (exencephally and microphthalia)

The need for submission of a Teratology study is indicated by above results.

Core Classifications:

"minimum" (interim report)

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