12-13-83

4/14/82 Toxicology Branch/RED Review

Caswell No(s).: 419F.

003434

To: Taylor/Walters

Registration No(s).:

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

Chemical(s): EL-107 50 W

Requested Action(s): EUP, non food use (new chemical

Recommendation: EUP can be toxicologically supported for non-food use.

Inert(s) cleared 180.1001: yes

% 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: none

RPAR status: none

New Data: See reviews attached

Data gaps: None for non-food EUP

Comments: Note that mutagenicity studies submitted with this EUP are still under review and do not affect this action.

10-31-83

Reviewer: W Thomas Edwards Date:

Section Head: William F Butler 12/12/83 Branch Chief: for ABS 12/13/83.

10 of 32

003434

TOXICOLOGY BRANCH

DATA REVIEW

Study Type: Acute oral toxicity in rats

Accession Number: 250791 (1)

MRID Number:

Sponsor: Eli Lilly and Company

Contracting Lab: Lilly Research Laboratories, Nos. RO-545-79 (females) and RO-546-79 (males)

Date: April 1981

Test Material: N-[3-(1-ethyl-1-methylpropyl)-5-isoxazolyl]-2,6-dimethoxybenzamide, formulation EL-107 50W

Protocol:

Five male and 5 female rats were each given a single oral dose of 500 mg/kg (EL-107 50W), 5% in 10% aqueous acacia solution.

Results:

There were no deaths.

"Signs of toxicity were limited to hindlimb paresis on the day of treatment in both sexes. All animals appeared normal 24 hours posttreatment and remained normal thorughout the subsequent 14-day observation period."

Conclusions:

Acute oral toxicity category: III

Core Classification:

Minimal

003434

TOXICOLOGY BRANCH DATA REVIEW

Study Type: Acute Dermal Toxicity and Dermal Irritation

Accession Number: 250791 (1)

MRID Number:

Sponsor: Eli Lilly and Company

Contracting Lab: Lilly Research Laboratories, Nos. B-D-169-79

Date: April, 1981

Test Material: N-[3-(1-ethyl-1-methylpropyl)-5-isoxazolyl]-2, 6-dimethoxybenzamide, formulation EL-107 50WP

Protocol:

Topical applications of 2000 mg EL-107 50W per kg were made to intact and abraded skin of6rabbits (1/2 abraded, 1/2 intact). Each sample was applied to a gauze pad and covered by an occlusive dressing and an adhesive sleeve. After 24 hours, coverings were removed and treatment sites were rinsed with warm water.

Results:

There were no deaths or evidence of systemic toxicity observed. Dermal irritation was limited to slight erythema in 3 rabbits that cleared within 7 days. The irritation index was 0.3 on a scale having a maximum of 8.0. LD_{50}: > 2000 mg/kg (HDT)

Conclusions:

A labelling category of III is appropriate for acute dermal toxicity and IV for primary dermal irritation.

Core Classification: Minimal

003434

TOXICOLOGY BRANCH DATA REVIEW

Study Type: Acute Eye Irritation

Accession Number: 250791 (1)

MRID Number:

Sponsor: Eli Lilly and Company

Contracting Lab: Lilly Research Laboratories, B-E-186-79

Date: April, 1981

Test Material: N-[3-(1-ethyl-1-methylpropyl)-5-isoxazolyl]-2, 6-dimethoxybenzamide, formulation EL-107 50W

Protocol:

Three male and 3 female rabbits were used. 33 mg (equivalent in volume to 0.1 cc) of EL-107 50W was placed in one eye of each rabbit, in a single application.

Results:

"Slight to moderate conjunctivitis, corneal dullness, and mild iritis, observed 1 hour after treatment, cleared within 7 days." One treated eye with a positive sodium fluorescein dye response at 24 hours was negative at 72 hours.

Conclusions:

The appropriate eye irritation category is II.

Core Classification: Guideline

OC-4

TOXICOLOGY BRANCH DATA REVIEW

Study Type: Acute Inhalation

Accession Number: 250791 (1)

MRID Number:

Sponsor: Eli Lilly and Company

Contracting Lab: Lilly Research Laboratories, R-H-88-79

Date: April, 1981

Test Material: N-[3-(1-ethyl-1-methylpropyl)-5-isoxazolyl]-2, 6-dimethoxybenzamide, formulation EL-107 50W

Protocol:

"Ten male and 10 female rats were exposed "head only" for one hour to a solid particulate aerosol of EL-107 50W. The nominal concentration was 7.9 mg of EL-107 50W per liter of air. The acute exposure concentration was 2.42 ± 0.26 (S.D.) mg of EL-107 50W per liter of air, with a range of 2.20 to 2.80 (gravimetric). The mass median equivalent aerodynamic diameter (MMEAD) was determined to be 3.68 um with a geometric standard deviation of 3.78."

Results:

One male and two females died during exposure. "Survivors appeared hypoactive immediately postexposure and for most of the exposure day. Surviving animals appeared normal within 24 hours and remained normal for the duration of the 14-day observation period. The one hour LC_{50} was greater than 2.42 ± 0.26 (S.D.) mg of EL-107 50W per liter of air."

Conclusions:

The acute inhalation toxicity category is III.

Core Classification: Minimal

OL-5

003434

TOXICOLOGY BRANCH DATA REVIEW

Study Type: Acute Oral Toxicity in Rats

Accession Number: 250791 (2).

MRID Number:

Sponsor: Eli Lilly and Company

Contracting Lab: Lilly Research Laboratories, Nos. R-O-48-81 (Females), R-O-49-81 (Males)

Date: April, 1981

Test Material: N-[3-(1-ethyl-1-methylpropyl)-5-isoxazolyl]-2, 6-dimethoxybenzamide, EL-107 (Lot B31-72C-88)

Protocol:

Ten male and 10 female rats were each given a single dose of 10,000 mg/kg by gavage (as a 30% suspension in 10% acacia) and observed for 14 days.

Results:

"No deaths occurred." "Signs of toxicity were limited to animals treated with EL-107 and consisted of generalized leg weakness and compound colored feces on the day of treatment. With the exception of soft stools which were observed in both treated and control animals after 8 days on test, all animals appeared normal 24 hours after dosing and for the remainder of the study." LD_{50}: >10,000 mg/kg for both males and females.

Conclusions: Acute oral toxicity category: IV.

Core Classification: Guideline

OL-6

003434

TOXICOLOGY BRANCH DATA REVIEW

Study Type: Acute Dermal Toxicity and Dermal Irritation

Accession Number: 250791 (3)

MRID Number:

Sponsor: Eli Lilly and Company

Contracting Lab: Lilly Research Laboratories. No. B-D-58-81

Date: September, 1981

Test Material: N-[3-(1-ethyl-1-methylpropyl)-5-isoxazolyl]-2, 6-dimethoxybenzamide, EL-107

Protocol:

Three rabbits per sex were treated. "The fur was clipped from the back of each animal and the exposed skin of one-half the animals in the test group was abraded with a stiff nylon brush. The abrasions were of sufficient depth to penetrate the stratum corneum but not to cause bleeding.

The test sample was applied undiluted to a gauze pad affixed to the treatment site with occlusive dressing and an adhesive sleeve. Occlusion was maintained for 24 hours."

"One hour after removal of the occlusive dressings, and twice daily for the subsequent 14 days, animals were examined for signs of toxicity. Individual body weights were recorded on the day the test substance was administered and weekly thereafter."

Results:

There was no evidence of dermal irritation during the study.
There was no evidence of systemic toxicity during the study.
LD_{50}: >200 mg/kg (HDT)

Conclusions:

Primary dermal irritation category: IV.
Acute dermal toxicity: dosage level inadequate.

Core Classification:

Primary dermal irritation: minimal.
Acute dermal toxicity: supplemental. ~~A NOEL was not determined.~~ MWB.

7

003434

D-7

TOXICOLOGY BRANCH DATA REVIEW

Study Type: Acute Eye Irritation

Accession Number: 250791 (3)

MRID Number:

Sponsor: Eli Lilly and Company

Contracting Lab: Lilly Research Laboratories, No. B-E-61-81

Date: September, 1981

Test Material: N-[3-(1-ethyl-1-methylpropyl)-5-isoxazolyl]-2, 6-dimethoxybenzamide, EL-107

Protocol:

"One eye of each of six rabbits (3 per sex) was treated with 28 mg (equivalent in volume to 0.1 cc) of undiluted test material. Prior to administration the test sample was triturated to a powder. The untreated eye of each animal served as control.

The test material was applied over the corneal surface and into the conjunctival cul-de-sac. The eyelids were held closed for several seconds after treatment to prevent expulsion of test substance.

Eyes were examined and ocular reactions were graded. Eyes were scored at 1, 24, 48, and 72 hours after dosing and again at 7 days. To aid in the identification of corneal lesions, sodium fluorescein dye was applied 24 hours after exposure."

Results:

"Corneal dullness and mild iritis in two animals and slight conjunctivitis in all animals were observed one hour after exposure. Irritation to the cornea and iris cleared within 24 hours, conjunctivitis cleared by three days postexposure." All rabbits exhibited a negative response to sodium fluorescein dye administered 24 hours after exposure. All treated eyes returned to normal within 72 hours of exposure.

Conclusions:

Eye irritation category: III.

Core Classification: Guideline

TOXICOLOGY BRANCH DATA REVIEW

Study Type: Acute Inhalation Toxicity

Accession Number: 250791 (3)

MRID Number:

Sponsor: Eli Lilly and Company

Contracting Lab: Lilly Research Laboratories, No. R-H-37-81

Date: September, 1981

Test Material: N-[3-(1-ethyl-1-methylpropyl)-5-isoxazolyl]-2, 6-dimethoxybenzamide, EL-107

Protocol:

"The ten male and ten female rats were restrained in acrylic "nose only" exposure tubes which were fitted to the ports of a 41 L cylindrical plexiglass exposure chamber and exposed for one hour. The mass median equivalent aerodynamic diameter (MMEAD) was determined to be 13.10 um with a geometric standard deviation of 3.53. The nominal concentration was 11.5 mg of 121607/L. The acute exposure concentration was 1.99 ± 0.199 (SD) mg of 121607/L, with a range of 1.68 to 2.22 mg of 121607/L".

Results:

There were no deaths. "All animals appeared normal immediately postexposure. One male rat exhibited rales on day 1 postexposure only. All animals appeared normal throughout the remainder of the 14-day postexposure observation period."
LC_{50}: >1.99 ± 0.199 mg/l, actual; 11.5 mg/l, nominal

Conclusions:

Acute inhalation category: II

Core Classification: Minimal

.OL-9

TOXICOLOGY BRANCH DATA REVIEW

Study Type: Acute Oral Toxicity in Mice

Accession Number: 250791 (4)

MRID Number:

Sponsor: Eli Lilly and Company

Contracting Lab: Lilly Research Laboratories, Nos. M-O-49-81 and M-O-50-81

Date: April, 1981

Test Material: N-[3-(1-ethyl-1-methylpropyl)-5-isoxazolyl]-2, 6-dimethoxybenzamide, EL-107

Protocol:

The acute oral toxicity was evaluated in 10 male and 10 female mice. Animals were observed for mortality and signs of toxicity for 14 days following a single 10,000 mg/kg oral dose of test compound (25% in a 10% aqueous acacia). The obsrvation period was 14 days.

Results:

There were no deaths. "In females signs of toxicity were confined to compound-colored feces 1 to 3 days after dosing in animals treated with compound 121607. Compound-colored feces was also observed 1 to 3 days after dosing in males treated with the test compound. In addition, an isolated instance of poor grooming was seen 24 hours after treatment and 3 to 10 male mice exhibited tail erection after 4 days on test. All animals appeared normal 5 days after dosing and for the remainder of the studies."

Gross pathology revealed no compound related lesions.
LD_{50}: >10,000 mg/kg in mice

Comments:

Acute oral toxicity category: IV.

Core Classification: Guideline

10

TOXICOLOGY BRANCH
DATA REVIEW

Study Type: Acute intraperitoneal toxicity in mice

Accession Number: 250791(5)

MRID Number:

Sponsor: Eli Lilly and Company

Contracting Lab: Lilly Research Laboratories, Nos. M-P-18-81 (females) and M-P-19-81 (males).

Date: April, 1981

Test Material: N-[3-(1-ethyl-1-methylpropyl)-5-isoxazolyl]-2,6-dimethoxybenzamide, EL-107

Protocol: Ten mice per sex per dose level were given orally 5.000 mg/kg or 20 ml/kg of vehicle. EL-107 was administered as a suspension containing 25% EL-107 in 10% aqueous acacia.

"Signs of toxicity were recorded at approximately one hour intervals for the first 6 hours after dosing, then daily for the subsequent 14 days of observation." "Gross pathology included an examination of the respiratory, cardiovascular, urogenital, musculoskeletal, lymphoreticular, endocrine, and digestive systems."

Results: There were no deaths from treatment.

"In females, signs of toxicity included generalized leg weakness, hypoactivity, tremors, and poor grooming. Generalized leg weakness was also observed in control females during the 2 hours following dosing. Signs of toxicity in males developed within 1 hour of dosing and included generalized leg weakness, hypoactivity, poor grooming, and tremors. Generalized leg weakness and poor grooming were observed in male control animals on the day of dosing. All animals, both compound-treated and control, appeared normal after 3 days on test and for the remainder of the study."

Gross pathology revealed compound-related "fibrinous adhesions were present in all animals injected intraperitoneally with compound 121607. Adhesions were present between the livers and the diaphragms, as well as between the intestines and the abdominal walls. In addition, numerous white aggregrates of unabsorbed compound were present within the omentums, on the serosal surfaces of the intestines, and on the surfaces of the livers. There was no evidence of compound-related systemic toxic effects."

003434

Conclusion: Acute intraperitoneal LD_{50} >5000 mg/kg

Core Classification: Acceptable

01-11

TOXICOLOGY BRANCH
DATA REVIEW

Study Type: Acute intraperitoneal toxicity in rats

Accession Number: 250791(6)

MRID Number:

Sponsor: Eli Lilly and Company

Contracting Lab: Lilly Research Laboratories, Nos. R-P-4-81 (females) and R-D-5-81 (males).

Date: April, 1981

Test Material: N-[3-(1-ethyl-1-methylpropyl)-5-isoxazolyl]-2,6-dimethoxybenzamide, EL-107

Protocol: Ten rats per sex per dose level were given by i.p. injection, 2,000 mg EL-107 per kg or 8 ml/kg of vehicle. EL-107 was administered as a suspension containing 25% EL-107 in 10% aqueous acacia.

"Signs of toxicity were recorded at approximately one hour intervals for the first 5 (males) to 6 (females) hours after dosing, then daily for the subsequent 14 days of observation."

A gross necropsy was performed on all animals that died during the study or survived to test termination. Gross pathology included an examination of the respiratory, cardiovascular, urogenital, musculoskeletal, lymphoreticular, endocrine, and digestive systems."

Results: There were no deaths from treatment.

"Signs of toxicity were similar in both studies and consisted of generalized leg weakness on the day of dosing in all compound-treated animals. In addition, instances of poor grooming and chromodacryorrhea were observed in female control animals 11 to 14 days after dosing."

"Compound-related fibrinous adhesions were present between the livers and the diaphragms in all animals injected. Numerous white aggregrates of unabsorbed compound were present within the omentums and on the surfaces of the livers. There was no evidence of compound-related systemic effects."

Conclusion: Acute intraperitoneal LD_{50} >2000 mg/kg

Core Classification: Acceptable

TOXICOLOGY BRANCH
DATA REVIEW

Study Type: Biliary excretion of radiocarbon in rats after single dose.

Accession Number: 250791(7)

MRID Number:

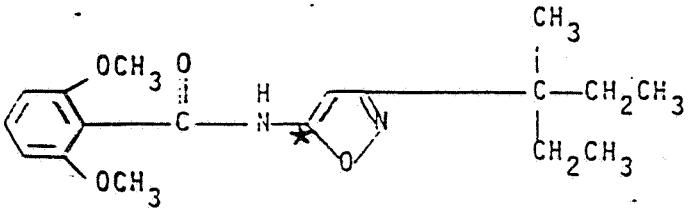
Sponsor: Eli Lilly and Company

Contracting Lab: Lilly Research Laboratories, Nos. R10582 & R11482

Date: December, 1981

Test Material: N-[3-(1-ethyl-1-methylpropyl)-5-isoxazolyl]-2,6-dimethoxybenzamide, EL-107 (92.4%) and ^{14}C-EL-107 (100%)

Chemical Structure:



*Indicates position of radiocarbon atom.

Protocol: "Single oral doses of [EL-107 spiked with ^{14}C-EL-107] were given to male and female Fischer 344 rats with exteriorized bile duct cannulae and the amount of radioactivity excreted into bile at 24-hours after dosing was determined. Five rats per sex were studied at 10 and 250 mg/kg to determmine if biliary excretion was dose dependent."

Results: Percent-of-dose biliary excretions are shown in Table 1 which was excerpted from the Eli Lilly report.

Discussion and Conclusion: Note the reduction in percent biliary excretion with increasing dose, especially in females. The decreased percent biliary excretion rates appear to be related to a rate-limiting gastro-intestinal absorption process, which is also indicated by the urine and fecal excretion studies (R07282 & R08882).

The biliary excretion difference between sexes is unexplained.

Core Classification: Acceptable

OL12

003434

TABLE 1

BILIARY EXCRETION OF RADIOCARBON FROM FISCHER 344 RATS GIVEN A SINGLE ORAL DOSE OF ^{14}C-EL-107

STUDIES R10582 and R11482

Animal Number	Study Number	Dose Group	Sex	Percent of Dose 0-24 Hr.
1001	R10582	10.0	M	16.9
1002			M	13.5
1003			M	27.8
1004			M	44.1
1005			M	13.4
Mean				23.1
S.E.				5.9
1051	R10582	10.0	F	39.8
1052			F	13.7
1053			F	38.6
1054			F	51.9
1055			F	49.8
Mean				38.8
S.E.				6.8
2001	R11482	250.0	M	23.6
2002			M	28.4
2003			M	11.8
2004			M	11.8
2005			M	11.8
Mean				17.5
S.E.				3.6
2051	R11482	250.0	F	20.7
2052			F	8.5
2053			F	26.3
2054			F	14.0
2056			F	6.9
Mean				15.3[a]
S.E.				3.7

[a] Significantly different from 10 mg/kg female group. Students t-test ($P \leq 0.05$).

OL-13

003434

TOXICOLOGY BRANCH
DATA REVIEW

Study Type: Radiocarbon excretion by rats after single oral doses.

Accession Number: 250791(8)

MRID Number:

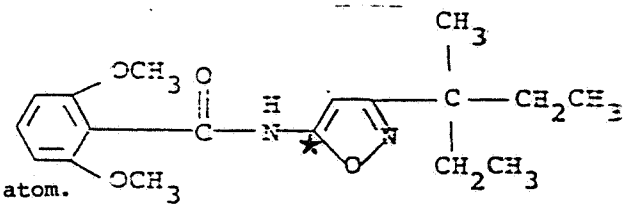
Sponsor: Eli Lilly and Company

Contracting Lab: Lilly Research Laboratories, Nos. R07282 & R08882

Date: December, 1981

Test Material: N-[3-(1-ethyl-1-methylpropyl)-5-isoxazolyl]-2,6-dimethoxybenzamide, EL-107 technical (92.4%) and ^{14}C-EL-107 (100%)

Protocol: "A sample of lot B31-72C-88 with a purity of 92.4% was used in this study. ^{14}C-EL-107, labeled in the isoxazole ring, was also used and was shown to have a radiochemical purity of 100% by thin layer chromatography and a specific activity of 11.21 uCi/mg. The structure of EL-107 is shown below:



*Indicates position of radiocarbon atom.

The dosage levels and extent of radioisotope spiking are shown in the following table.

"Animal Number	Dose	^{14}C Dose	Dose Volume
1051-1055	10 mg/kg	14 uCi/kg	10 ml/kg
2051-2055	100	"	"
3051-3055	250	"	"
4051-4055	500	"	"
5051-5055	1000	"	"

Doses were given as microsuspensions in 10% acacia solutions.

The urinary and fecal excretion of radioactivity was measured for three successive 24-hour periods.

Results:

Figures 1 (males) and 2 (females) attached present by bar graph the cumulative percentage excretion of radiolabeled EL-107. These figures were excerpted from Eli Lilly's report.

Discussions and Conclusions: It is noted, from each dosage level that most of the excretion of EL-107 occurred within 24 hours and that very little more was excreted by the 72nd hour.

Fecal excretion was the major elimination route.

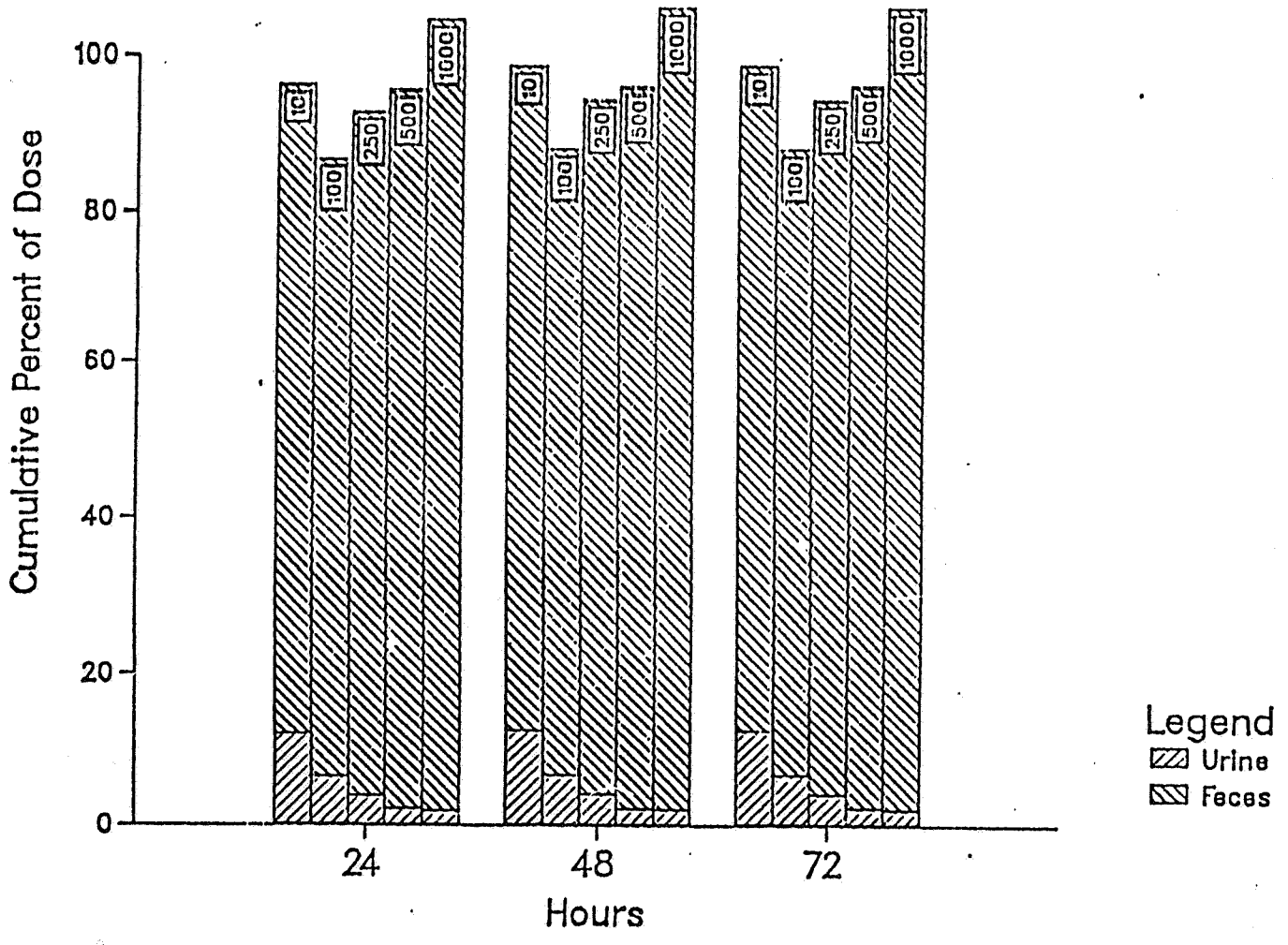
It appears that gastro-intestinal absorption is a rate-limiting process. This is indicated by dose related decreasing ratios of urinary excretion to fecal excretion.

"By the end of the collection periods, the mean percent of the radiolabeled dose excreted in urine and feces ranged from 70.8 to 94.9% in males and from 88.2 to 106.3% in females."

Core Classification: Acceptable

FIGURE 2

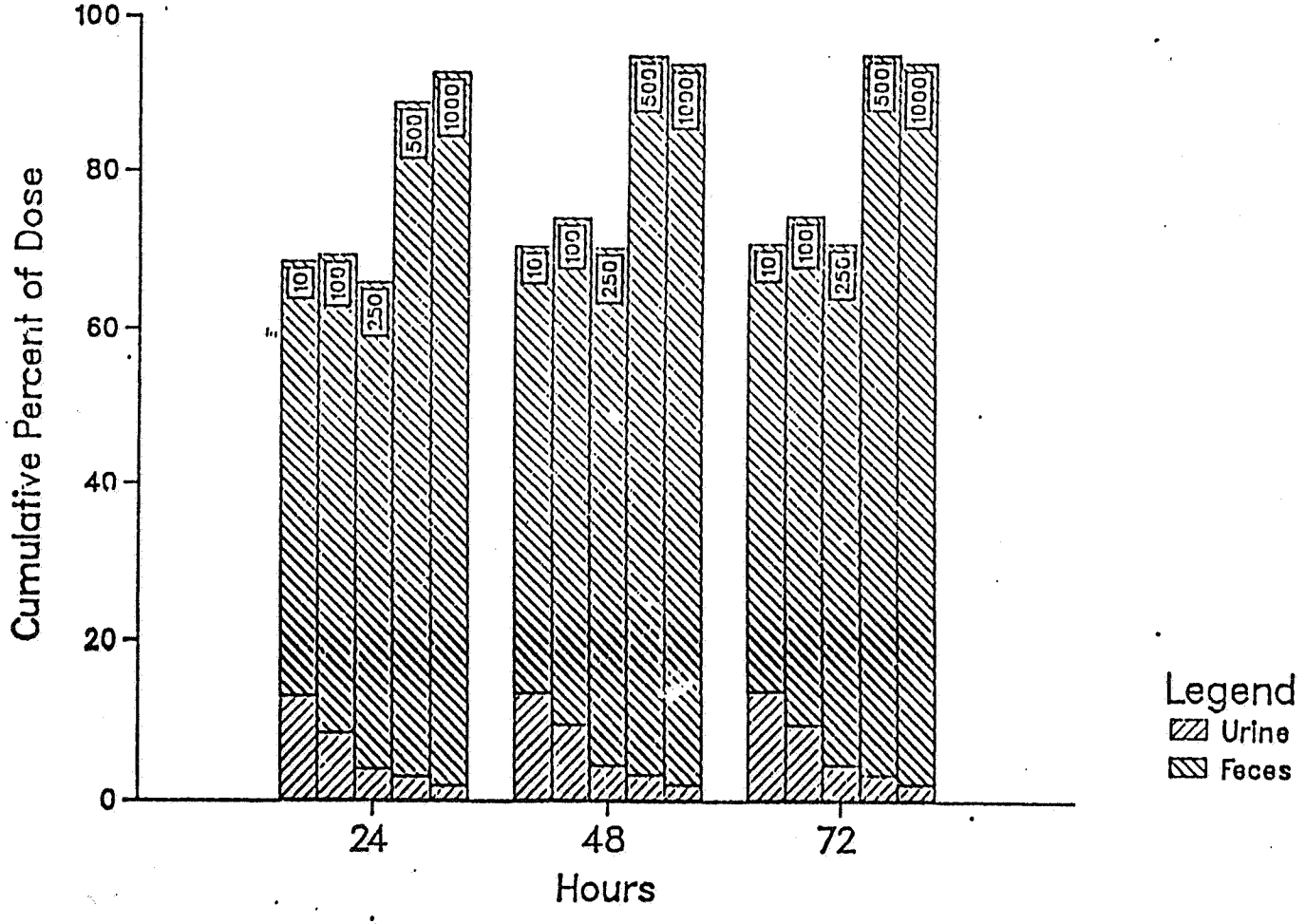
Cumulative Excretion of Radioactivity in Female Rats Receiving a Single Oral Dose of Radiolabeled EL-107. Study R08882.



* Doses Indicated Within Bars are in mg/kg

FIGURE 1

Cumulative Excretion of Radioactivity in Male Rats Receiving a Single Oral Dose of Radiolabeled EL-107. Study R07282.



* Doses Indicated Within Bars are in mg/kg

TOXICOLOGY BRANCH

DATA REVIEW

Study Type: Tissue distribution of radiocarbon in rats after single oral doses

Accession Number: 250791 (9)

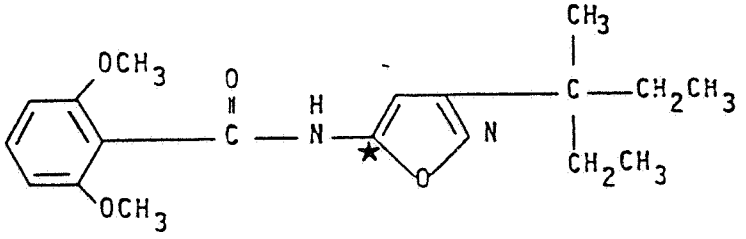
MRID Number:

Sponsor: Eli Lilly and Company

Contracting Lab: Lilly Research Laboratories, Nos. R05082 & R06182.

Date: December 1982

Test Material: N-[3-(1-ethyl-1-methylpropyl)-5-isoxazolyl]-2,6-dimethoxybenzamide, EL-107 (92.4%) and ^{14}C-EL-107 (100%)
The structure of EL-107 is shown below:



*Indicates position of radiocarbon atom.

Protocol:

"Rats were given single oral doses of radiolabeled EL-107 equal to 250 mg/kg. Each animal received a constant volume of dose suspension based on body weight (10 ml/kg). A total of five rats per sex per sampling time was utilized. After dosing, the rats were placed in individual cages and allowed free access to water. Food was withheld until four hours after dosing.

At 4 or 24 hours after dosing the animals were anesthetized with ether and after laparotomy a blood sample was obtained from the abdominal aorta. The animals were killed by cervical dislocation, and tissues and organs were removed."

"The microgram equivalents of [^{14}C]-EL-107 per gram of each tissue (or per ml for plasma) and the tissue to plasma ratios were calculated."

Results:

Tissue levels of radiocarbon measured in male and female rats are presented in Tables 1 and 2 respectively (as excerpted from the report).

Discussions and Conclusions:

When comparing concentrations found after 24 hours with those found after 4 hours, it was noticed that there were large increases in ratios of tissue to plasma levels (whether expressed as MCG-EQ/G or as % increases) in adrenals, eyes, thyroid, pituitary, and ovaries. There were also increases of lesser amounts of concentration in some other organs. The largest increases were in female pituitaries, from a ratio of 1.75 to 20.55, an increase of 18.80 MCG-EQ/G or 1074%.

Differences between sexes were striking; the larger changes were found in females. For example the average relative increase in male pituitaries was from 12.09 to 14.71, 2.02 MCG EQ/G or 15.9% (refer to female results above.)

Twenty-four hours was not long enough for maximum values to be demonstrated in several organs or for decreases in the organs to be observed.

A longer-term distribution study could better elucidate persistence and storage in organs.

Core Classification: Acceptable

TABLE 1. CONCENTRATION AND TISSUE-TO-PLASMA RATIOS OF RADIOACTIVITY IN TISSUES FROM MALE RATS GIVEN ORAL DOSES OF 250 MG/KG OF RADIOLABELED 121607. STUDY R05082

	HOURS AFTER DOSING					
	4			24		
TISSUE	MCG-EQ/G		TISSUE/ PLASMA	MCG-EQ/G		TISSUE/ PLASMA
LIVER	23.75 ±	1.672	14.63	3.78 ±	0.272	7.37
KIDNEY	8.07 ±	0.925	4.93	2.06 ±	0.233	4.03
BRAIN	0.65 ±	0.033	0.41	0.16 ±	0.023	0.31
HEART	1.20 ±	0.037	0.75	0.30 ±	0.060	0.58
LUNG	1.93 ±	0.535	1.13	0.37 ±	0.030	0.71
ADRENALS	4.66 ±	0.386	2.91	1.70 ±	1.003	3.80
EYES	1.24 ±	0.193	0.77	0.43 ±	0.053	0.86
SPLEEN	1.08 ±	0.054	0.67	0.30 ±	0.030	0.59
PLASMA *	1.64 ±	0.146	1.00	0.52 ±	0.029	1.00
MUSCLE	0.74 ±	0.092	0.48	0.22 ±	0.018	0.43
FAT	2.00 ±	0.108	1.27	0.47 ±	0.030	0.91
DUODENUM	8.40 ±	0.592	5.22	1.30 ±	0.184	2.61
JEJUNUM	17.84 ±	3.931	10.96	1.93 ±	0.089	3.81
ILEUM	63.85 ±	19.066	40.37	3.34 ±	0.643	6.71
COLON	21.49 ±	11.414	13.19	4.09 ±	0.805	7.83
THYROID	27.03 ±	19.931	18.27	2.11 ±	0.316	4.15
THYMUS	0.69 ±	0.017	0.43	0.25 ±	0.021	0.49
PANCREAS	1.31 ±	0.061	0.82	0.36 ±	0.020	0.71
PITUITARY	18.02 ±	7.557	12.69	7.82 ±	3.903	14.71
PROSTATE	10.27 ±	5.730	5.69	1.15 ±	0.361	2.31
TESTES	0.51 ±	0.022	0.32	0.17 ±	0.009	0.34

* PLASMA VALUE EXPRESSED AS MCG-EQ/ML

EACH VALUE IS EXPRESSED AS THE MEAN ± S.E. FOR N=5 RATS

TABLE 2. CONCENTRATION AND TISSUE-TO-PLASMA RATIOS OF RADIOACTIVITY IN TISSUES FROM FEMALE RATS GIVEN ORAL DOSES OF 250 MG/KG OF RADIOLABELED 121607. STUDY R06182

	HOURS AFTER DOSING					
	4			24		
TISSUE	MCG-EQ/G		TISSUE/ PLASMA	MCG-EQ/G		TISSUE/ PLASMA
LIVER	25.40 ±	1.836	11.06	3.49 ±	0.561	8.04
KIDNEY	10.40 ±	0.800	4.49	2.20 ±	0.365	4.92
BRAIN	0.67 ±	0.051	0.29	0.48 ±	0.121	0.97
HEART	2.43 ±	0.426	1.09	0.61 ±	0.129	1.35
LUNG	1.86 ±	0.297	0.82	0.56 ±	0.112	1.19
ADRENALS	5.79 ±	1.262	2.48	2.87 ±	0.540	6.50
EYES	0.67 ±	0.066	0.29	1.05 ±	0.298	2.28
SPLEEN	1.31 ±	0.102	0.57	0.57 ±	0.087	1.37
PLASMA *	2.32 ±	0.132	1.00	0.47 ±	0.096	1.00
MUSCLE	3.30 ±	2.013	1.39	0.36 ±	0.060	0.80
FAT	5.98 ±	0.480	2.58	1.16 ±	0.212	2.65
DUODENUM	8.91 ±	0.557	3.89	1.63 ±	0.465	3.35
JEJUNUM	22.25 ±	7.391	9.17	2.50 ±	0.572	5.65
ILEUM	56.78 ±	7.577	25.02	3.64 ±	0.700	8.34
COLON	7.18 ±	2.892	3.23	5.73 ±	1.057	12.61
THYROID	3.22 ±	0.931	1.36	3.44 ±	0.284	8.54
THYMUS	1.48 ±	0.162	0.65	0.35 ±	0.050	0.79
PANCREAS	2.57 ±	0.230	1.11	0.42 ±	0.075	0.92
PITUITARY	4.28 ±	2.185	1.75	8.53 ±	2.389	20.55
OVARIES	2.24 ±	0.126	0.98	1.58 ±	0.347	3.53
UTERUS	1.43 ±	0.075	0.63	0.84 ±	0.130	1.92

* PLASMA VALUE EXPRESSED AS MCG-EQ/ML

EACH VALUE IS EXPRESSED AS THE MEAN ± S.E. FOR N=5 RATS

DL-15 1

003434

TOXICOLOGY BRANCH DATA REVIEW

Study Type: Three-months oral administration in dogs

Accession Number: 250791 (10)

MRID Number:

Sponsor: Eli Lilly and Company

Contracting Lab.: Lilly Research Laboratories, No. D33582

Date: December, 1982

Test Material: N-[3-(1-ethyl-1-methylpropyl)-5-isoxazolyl]-2,6-dimethoxybenzamide, EL-107 (lot no. H02-2G6-021).

Protocol: "Four groups of dogs, each consisting of four males and four females, received either 0, 0.25, 0.5, or 1.0 g/kg of compound EL-107 daily for three months," administered in gelatin capsule once each day. Dogs were observed for behavior and physical signs, several times daily during the week and at least once daily on weekends and holidays.

"Ophthalmoscopic and physical examinations were performed by a veterinarian prior to study initiation and at the termination of the study.

"The hematologic parameters examined were: Packed cell volume (PCV), hemoglobin (HGB), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), erythrocyte count (RBC) and morphology, total and differential leukocyte counts (WBC), activated partial thromboplastin time (APTT), platelet count, and reticulocyte count. A cytologic evaluation of bone marrow smears including an estimated M:E ratio was performed at termination of the study.

"The following clinical chemistry parameters were determined: glucose (GLU), urea nitrogen (BUN), creatinine (CREAT), total bilirubin (T.B.), and activities of the enzymes alkaline phosphatase (A.P.) and alanine transaminase (ALT, SGPT).

"Urine samples were collected for urinalysis at pretreatment, 1, 2, and 4 weeks, and monthly thereafter. Urine specific gravity, glucose content, pH, protein content, occult blood, color, and clarity were measured.

"Hepatic p-nitroanisole O-demethylase activity was determined for all dogs using a portion of the liver collected at necropsy.

"The weights of the following organs were recorded at necropsy: liver, kidneys, heart, thyroids, adrenals, testes or ovaries. Organ to body weight ratios were calculated."

Histopathological examinations of the following organs were made:

"Kidney, liver, heart, lung, spleen, thymus, lymph node, salivary gland, pancreas, stomach, duodenum, jejunum, ileum, colon, ovary, uterus, adrenal, thyroid (with parathyroid), gallbladder, testis, prostate, skin, mammary gland, skeletal muscle, urinary bladder, bone, bone marrow, eye, cerebrum, cerebellum, brain stem, pituitary, and gross lesions."

Results: There were no deaths.

"Many dogs in the middle (0.5 g/kg) and high-dose (1.0 g/kg) groups intermittently vomited food and/or test compound. Feces from some animals occasionally were mucoid, pale or contained test compound. These findings were attributed to the large volume of test material administered and not to any intrinsic toxicity of the compound.

"No treatment-related abnormalities were found during physical or ophthalmoscopic examinations conducted prior to necropsy.

"One high-dose (1.0 g/kg) male lost 10% of its initial body weight during the test but had regained some of the loss by the end of the test. No other dogs had significant body weight changes. There were no observed changes in food consumption."

There were no changes in hematologic parameters that could be ascribed to treatment. Bone marrow evaluation revealed no abnormalities.

The report presents individual animal data for changes of clinical parameters. No summaries by dosage level groups were included. However, it is noted that alkaline phosphatase for control animals decreased with time, amounting to mean decreases of 57% for males and 55% for females. No similar decreases were seen for treated groups.

The attached tabulation shows the relative concentrations of the treated, both at start and finish, as compared to controls. Values are shown separately for males and females as well as for males and females combined. Also shown are percent relative changes, as compared to controls, for each dosage level.

It is apparent that treatment effects are shown at each treatment level. There were no changes in urinalysis results which indicated treatment effects.

No gross pathological lesions were reported.

No biologically important changes in absolute or relative organ weights were observed. Enzyme induction (as assessed by determining the activity of hepatic p-nitroanisole O-demethylase) was found at all dosage levels in both males and females.

003434

"Minimal centrilobular hypertrophy of hepatocytes was noted in one high-dose and one middle-dose male. This was considered to be treatment related. No other compound-related lesions were present."

Conclusions: A NOEL was not determined. Treatment related effects included centrilobular hypertrophy of hepatocytes in one high-dose (1.0 .g) male and one middle-dose (0.5 g/kg) male, relative increases of serum alkaline phosphatase at all dosage levels, and also at all dosage levels the induction of hepatic microsomal enzymes as demonstrated by the p-nitroanisole O-demethylase test.

Core Classification: ~~Supplemental. A NOEL was not determined.~~ Minimum Data NOEL is ~~test~~ < 0.25 ~~mg~~ Gm/kg (LDT) (ry) WMButtles

Relative concentrations of serum alkaline phosphatase

Dosage groups	Concentration at start relative to controls			Concentration at finish relative to controls			Percent relative increase		
	M	F	M+F	M	F	M+F	M	F	M+F
Control	1.0	1.0	1.0	1.0	1.0	1.0	0	0	0
0.25 g/kg	0.905	1.05	0.972	1.64	2.27	1.96	+81	+117	+102
0.50 g/kg	0.966	1.28	1.12	1.57	2.03	1.80	+62	+59	+61
1.0 g/kg	0.852	0.926	0.871	2.64	1.87	2.26	+210	+102	+159

OL-16

003434

TOXICOLOGY BRANCH

DATA REVIEW

Study Type: Three-months feeding in rats

Accession Number: 250792 (11)

MRID Number:

Sponsor: Eli Lilly and Company

Contracting Lab: Lilly Research Laboratories, No. R00182

Date: December 1982

Test Material: N-[3-(1-ethyl-1-methylpropyl)-5-isoxazolyl]-2,6-dimethoxybenzamide, EL-107 technical (Lot B31-72C-88), 92.4%

Protocol:

"Rats in groups of 15 males and 15 females were maintained on diets containing 0, 1.25, 2.5, or 5.0% of EL-107, for three months. The dietary concentrations resulted in the time weighted average daily dose of 905, 1813, or 3701 mg/kg for males and 964, 1939, or 3962 mg/kg for females of active compound."

"Just prior to necropsy, the test animals were anesthetized with ether and blood samples were obtained by cardiac puncture. Hematologic parameters evaluated on all animals included: erythrocyte count, hemoglobin, packed cell volume (PCV), total and differential leukocyte counts, erythrocyte morphology, mean cell volume (MCV), mean cell hemoglobin (MCH) and mean cell hemoglobin concentration (MCHC)."

"Clinical chemistry parameters determined on all rats at the conclusion of this study included: serum concentrations of glucose, urea nitrogen, creatinine, total bilirubin, and activities of the enzymes alkaline phosphatase and alanine transaminase (ALT)."

"Enzyme induction by EL-107 was assessed by determining the activity of hepatic p-nitroanisole O-demethylase. At the time of necropsy, liver samples weighing approximately two grams each were obtained from five animals of each sex at each dose level. Liver homogenates were prepared and p-nitroanisole O-demethylase activity was measured."

"During necropsy weights were recorded for the following organs: adrenals, heart, kidneys, liver, ovaries, spleen, testes, and thyroids. Relative organ weights were also calculated (organ weight:body weight ratio)."

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

Histopathologic examination included the following: kidney, liver, heart, lung, spleen, thymus, lymph node, salivary gland, pancreas, stomach, duodenum, jejunum, ileum, colon, ovary, uterus, adrenal, thyroid (with parathyroid), testis, prostate, skin, mammary gland, skeletal muscle, urinary bladder, bone, bone marrow, eye, cerebrum, cerebellum, brain stem, pituitary, and gross lesions.

Results:

There were no deaths.

There were no physical signs of toxicity.

Changes in mean hematological values were not large and are considered to be of little if any biological significance.

Decreased mean alkaline phosphatase levels were found for all dosage levels and were apparently dose related. The two higher dosage values were statistically significant. Mean creatinine levels were statistically decreased in females at all levels. Also found were statistically decreased alanine transaminase in females of the highest level and statistically increased means of blood glucose in females of the high level. The biological significance of these changes is unclear.

"Statistically significant increases in hepatic p-nitroanisole O-demethylase activity were noted in both males and females receiving low (1.25%) and middle-dose (2.5%) diets and in females receiving high-dose (5.0%) diets. High-dose (5.0%) males also had higher values than controls, but this increase was not statistically significant."

No gross treatment related lesions were reported.

"Statistically significant increases in absolute and relative liver weights occurred in both males and females at all dose levels. Statistically significant increases in relative kidney weights occurred in both males and females receiving the low-dose (1.25%) and middle-dose (2.5%) diets. The increase in relative kidney weights for both males and females of the high-dose (5.0%) was not significant.

"No treatment-related effects were noted in absolute or relative (to body weight) heart, spleen, thyroids (parathyroids), adrenals, testes or ovaries weights at the termination of the study."

Conclusions:

A NOEL was not determined (LDT, 1.25%). Effects noted at all dosage levels were: increases in absolute and relative liver weights, increases in relative kidney weights, and induction of hepatic enzymes. Note that this study is followed by a similar study using lower dosage levels.

29

This study was well performed but if considered alone is inadequate for regulatory purposes. See also the succeeding study R12582.

Core Classification:

~~Supplemental~~ MINIMUM ~~PASS~~ NOEL < 1.25% (L.D.T.) with Butter

003434

DL-17

TOXICOLOGY BRANCH

DATA REVIEW

Study Type: Three-months feeding study in rats with one-month recovery. Interim report.

Accession Number: 250792 (12)

MRID Number:

Sponsor: Eli Lilly and Company

Contracting Lab: Lilly Research Laboratories, No. R12582

Date: March 1983

Test Material: N-[3-(1-ethyl-1-methylpropyl)-5-isoxazolyl]-2,6-dimethoxybenzamide, EL-107 Technical (Lot No. H02-2G6-118, 78% EL-107)

Protocol:

Twenty-five rats per sex per group were fed 0, 0.05, 0.14. 0.42, 1.25% EL-107 for 3 months, after which 10/sex/group were observed during a 1-month reversibility period during which time they received no additional EL-107. The dosages were equivalent to "a time weighted daily dose of 32.3, 95.7, 285.0, or 852.6 mg/kg/day for males and 36.1, 104.1, 311.9, or 945.8 mg/kg/day for females."

"Test animals were examined daily for general physical condition and behavior. A detailed examination was performed weekly in which muscle tone, condition of pelage, color and appearance of eyes, respiration, posture, excreta, locomotion, and presence of external lesions or growths were evaluated."

"During necropsy, weights were recorded for the following organs: adrenals, heart, kidneys, liver, ovaries, prostate, spleen, testes, thyroids, and uterus. Relative organ weights were also calculated (organ weight:body weight ratio)."

"Enzyme induction by compound EL-107 was assessed by determining the activity of hepatic p-nitroanisole O-demethylase. At the time of necropsy, liver samples weighing approximately two grams each were obtained from five animals of each sex at each dose level. Liver homogenates were prepared and p-nitroanisole O-demethylase activity was measured."

15 animals per sex per group were killed after the three-months treatment period and 10 after the 1-month recovery period.

Results:

"This interim report contains all of the data that is available following the live phase of the study. The gross, microscopic and clinical pathology results will be submitted as soon as they are completed."

"There were no mortalities during either the treatment or recovery phases." "No physical signs of toxicity were observed during either the treatment or recovery phases."

"In the treatment phase statistically significant increases occurred in relative testis and liver weights in males of the 0.42 and 1.25% dose groups; relative kidney weight in males of the 1.25% dose group; and both absolute and relative liver weights in females of all dose groups.

In the treatment phase, statistically significant decreases occurred in both absolute and relative spleen weights of males in all dose groups, except for the 0.42% group, where only the absolute value was significant."

"In the reversibility phase weights of organs affected at three months, except for relative liver weight in the 1.25% males, were similar to control values. The absolute heart weight decrease in the 0.42 and 1.25% females, and relative heart weight decrease in the 0.05% females during the reversibility phase were not considered to be biologically significant." After 3-months hepatic p-nitroanisole O-demethylase activity was increased in all treated rats, male and female. Increases were statistically significant ($p \leq 0.05$) for males at the 0.42 ppm dosage levels and for females at 0.14 ppm and higher levels.

After the one-month recovery period, the above induced enzyme levels in females returned to normal. Male levels were reduced to below control levels in a dose-related manner.

Conclusions:

A NOEL was not determined. EL-107 effects were found at all dosage levels including the lowest (0.05 %). The following effects were noted at the lowest level tested: absolute and relative weights of liver and spleen and also hepatic enzyme induction. This interim report is incomplete because pathology has not been received. It is also inadequate to meet our minimal needs because a NOEL was not determined. The study does have supplemental value.

Core Classification:

Supplemental