

DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

ISOXABEN

Chemical Code # 2289, Tolerance # 51631
SB 950 # (N/A)

Original date: 5/7/91

Revised date: 9/25/91

I. DATA GAP STATUS

Combined, rat:	See chronic or oncogenicity, below
Chronic toxicity, rat:	No data gap, no adverse effects
Chronic toxicity, dog:	No data gap, no adverse effects
Oncogenicity, rat:	No data gap, possible adverse effect
Oncogenicity, mouse:	No data gap, possible adverse effect
Reproduction, rat:	No data gap, no adverse effects
Teratology, rat:	No data gap, no adverse effects
Teratology, rabbit:	No data gap, no adverse effects
Gene mutation:	No data gap, no adverse effects
Chromosome effects:	No data gap, possible adverse effect
DNA damage:	No data gap, no adverse effects
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

All record numbers through 89663 (Document 51631-024) were examined (i.e., all records on file with CDPR as of 9/25/91).

In the record number designations for the one-liners below:

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

indicates a study on file but not yet reviewed.

File name: T910925

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

COMBINED, RAT

51631-013 (3 parts) **075360** Lake, S.G., McGrath, J.P., and Usher, R.W. "A two-year toxicity/oncogenicity study of EL-107 administered in the diet to Fischer 344 rats". Lilly Research Laboratories, Greenfield, IN., Nov., 1985: Study Replicates R01583 and R01683. EL-107 was 85% Lilly compound 121607 (isoxaben). Two closely-related isomers comprised an additional 10.5% of test article. Dosage groups received 0, 125, 1250, or 12,500 ppm in diet for 2 years. There were 60 rats/sex/group [two replicate studies with 30/sex/group]. A conservative NOEL is 125 ppm (about 5 mg/kg/day), based on apparent increases in progressive glomerulonephrosis in mid-dose males, which findings were clearly elevated in high dose males and females. Other findings at the high dose level in both sexes included slightly decreased body weights, elevated blood cholesterol levels, and increased kidney and liver weights. Major findings in high dose males included: increased mortality (late in study), clinical chemistry changes (elevated BUN, creatinine, phosphorous - all considered related to kidney effects), minor but consistent hematology changes (reduced RBC counts, reduced HCT), stomach mucosal mineralization and parathyroid hyperplasia (both plausibly related to progressive glomerulonephrosis). **Possible adverse effect:** increased incidence of a common tumor (pheochromocytoma) in high dose males compared to combined other groups (incidence of 10, 9, 9, and 18 in controls, low, medium, and high dose groups, respectively). **Acceptable for oncogenicity data requirement: not acceptable, but upgradeable toward chronic study data requirement.** Aldous, 5/6/91.

CHRONIC TOXICITY, RAT

** 024; 89627; "A Final Report on a Chronic Toxicity Study of EL-107 Administered in the Diet to Fischer 344 Rats for up to One Year" (Lilly Research Laboratories, Greenfield, IN, Study # R01483, 12/12/85); 831; EL-107 (Lot # Z10025, 95.5% purity); actual mean dose levels: 0, 6.6, 65.8, or 670.4 mg/kg/day to 30 Fischer 344 rats/sex/dose; 10 rats/sex/dose terminated at 3, 6, and 12 months for interim examinations; **no adverse effects**; all animals survived the entire treatment period without any overt physical signs of toxicity; increases in hepatic p-nitroanisole O-demethylase activity in high-dose males (34.1 - 34.9% of control, $p < 0.05$) and females (57.0 - 87.8%, $p < 0.05$) and in mid-dose females (28.9 - 35.8%, $p < 0.05$) at 6 months and 1 year; elevated liver weight in high-dose males (12.6 - 28.6% of control, $p < 0.05$) and females (9.2 - 24.8% of control, $p < 0.05$) at all three time intervals and mid-dose males (15.5% of control, $p < 0.05$) at 6 months; no compound-related lesions were present in any animals after 3, 6, or 12 month treatment with EL-107; NOEL (M/F) = 6.6 mg/kg/day (elevated liver weight and p-nitroanisole O-demethylase activity); **acceptable**; (Leung, 9/23/91).

CHRONIC TOXICITY, DOG

** 012; 024; 075359; 89663; "A one-year toxicity study of EL-107 administered orally to beagle dogs". Lilly Research Laboratories, Greenfield, IN., Dec., 1985, Study D04783. EL-107 was 85% Lilly compound 121607 (isoxaben). Dosages of 10, 100, and 1000 mg/kg/day, administered daily by gelatin capsule to 4 beagles/sex/dose for one year. No adverse effects. Some findings of no apparent toxicologic consequence were observed in low dose animals (soft

stools and/or diarrhea appeared to be slightly elevated in 10 mg/kg/day males; alkaline phosphatase appeared to be slightly elevated in 10 mg/kg/day females). Thus no clear NOEL was established. An overall NOAEL of 10 mg/kg/day could be established, since findings of toxicologic consequence were limited to the higher two dosages. Liver was apparent primary target. Noteworthy liver effects included: slight liver enlargement (ca. 20%) in both sexes at 1000 mg/kg/day, "minimal hypertrophy" in two of four 1000 mg/kg/day females, and alkaline phosphatase elevations in both sexes during the latter months of the study at 100 and 1000 mg/kg/day. originally reviewed as **Not acceptable** but **possibly upgradeable** with assurance that parathyroids were examined (Aldous, 5/7/91); study rereviewed with indication that parathyroid glands were examined without any abnormal findings; **acceptable**; (upgraded; Leung, 9/18/91).

ONCOGENICITY, RAT

(see combined, rat, above)

ONCOGENICITY, MOUSE

****51631-011** (3 parts) **075358** Lake, S.G., and Usher, R.W. "A two-year chronic oncogenic toxicity study of EL-107 administered in the diet to B6C3F1 mice". Lilly Research Laboratories, Greenfield, IN., 11/85. Study Replicates M00883 and M00983. EL-107 was 85% Lilly compound 121607 (isoxaben). Two closely-related isomers comprised an additional 10.5% of test article. Dosage groups of 0, 100, 1000, and 12,500 ppm in diet for 2 years to 60 mice/sex/group [two replicate studies with 30/sex/group]. **Possible adverse effect**: increased incidence and multiplicity of hepatocellular adenomas in 12,500 ppm males and females. Increased hepatocellular hyperplasia at that level in both sexes, also cytomegaly at that level (particularly in males). No increases in hepatocellular carcinomas. NOEL = 100 ppm, based primarily upon increased incidence and degree of hepatocellular vacuolation in males and females at 1000 ppm and 12,500 ppm. **Acceptable**. Aldous, 1/30/90.

REPRODUCTION, RAT

****51631-015** (2 parts) **075363** "A three-generation reproduction study with EL-07 in the Wistar rat". Lilly Research Laboratories, Greenfield, IN., August, 1984. Dietary administration of 0, 500, 2500, or 12,500 ppm of EL-107 (85% a.i.: same lot as was used in contemporary rodent and dog chronic studies). Two litters per generation for F0 and F1 parents were raised through weaning. Twenty-five pairs/group were allocated for the above trials and for production of F2c fetuses in the first of two teratology trials. A second teratology trial was performed in which F2b parents produced F3 fetuses: in this case there were small ancillary control and 12,500 ppm groups to evaluate possible hereditary factors. Parental toxicity NOEL = 500 ppm (maternal body weight and weight gain decrements during growth period: maternal liver weights elevated). Reproductive effects NOEL = 2500 ppm (elevated microphthalmia or anophthalmia, often accompanied by exencephaly and/or other craniofacial malformations: decreased ovulation (reduced corpora lutea counts): reduced weight gain in lactating pups (possibly associated with reduced or eliminated milk production in dams). Not classified as a "possible adverse effect", due to evidence of maternal toxicity at levels which elicit reproductive effects, and because there was a high reproductive effects NOEL. **Acceptable**. C. Aldous, 2/20/90.

TERATOLOGY, RAT

51631-014 075362 "A teratology study of EL-107 administered orally to Wistar rats". Lilly Research Laboratories, Toxicology Division, Greenfield, IN. July, 1984. The test article, EL-107, was 85% isoxaben; 10.5% of the balance was two closely related isomers (lot Z10025). 25 dams/dose at levels of 0, 100, 320, and 1000 mg/kg/day. The NOEL = 320 mg/kg/day, based on a slight increase in early resorptions in the high dose group of this study and in the comparable high dose groups of teratology segments of the contemporary reproduction study in Vol. 015. **Acceptable. No adverse effects, since there is a comparatively high NOEL, and because maternal toxicity has already been identified in a reproduction study at dosages comparable to the LEL of the present study. C. Aldous, 2/23/90.

TERATOLOGY, RABBIT

51631-014 075361 "A teratology study of EL-107 administered orally to Dutch Belted rabbits". Lilly Research Laboratories, Toxicology Division, Greenfield, IN. May, 1984. The test article, EL-107, was 85% isoxaben; 10.5% of the balance was two closely related isomers (lot Z10025). Twenty dams/dose at levels of 0, 100, 320, and 1000 mg/kg/day. **Acceptable. No adverse effects: maternal NOEL = 320 mg/kg/day (one high dose death and one high dose abortion, both of which followed periods of anorexia, may have been treatment-related). No developmental toxicity was observed. C. Aldous, 2/21/90.

GENE MUTATION

016 075364 "The Effect of EL-107 (Compound 121607) on the Induction of Bacterial Mutation Using a Modification of the Ames Test." (Lilly Research Laboratories, 12/82) Isoxaben, lot HO2-2G6-118 (85.4% EL-107, 8.8% Compound 135520 - structural isomer); tested with Salmonella typhimurium, strains G46, TA1535, TA1537, TA1538, TA98, TA100, C3076 and D3051; Escherichia coli strains WP2 and WP2uvrA; gradient plate protocol testing with and without Aroclor 1254-induced rat liver activation, 1 plate each with 0.1 - 1, 1 - 10, 10 - 100 or 100 - 1000 µg/ml; all strains streaked across the same plate; report states no cytotoxicity and no evidence for mutagenicity. **No adverse effect. Unacceptable**, not upgradeable (protocol semiquantitative only). (Gee, 2/9/90)

016 075365 "The Effect of EL-107 (Compound 121607) on the Induction of Forward Mutation at the Thymidine Kinase Locus of L5178Y Mouse Lymphoma Cells." (Toxicology Division, Lilly Research Laboratories, Greenfield, IN, Study 820928MLA1378, 12/82) EL-107, Isoxaben, lot HO2-2G6-118 (85.4% EL-107, 8.8% Compound 135520 - structural isomer); tested with mouse lymphoma L5178Y TK^{+/+} cells with and without Aroclor 1254-induced rat liver activation, 3% final; with activation at 0, 0.5, 1, 2, 4, 6, 8, 10 or 12 µg/ml and without activation at 0, 1, 10, 50, 75, 100, 150, 200 or 250 µg/ml, both with 4 hour treatment followed by 48 hour expression; single culture per concentration, single trial; triplicate plates for mutation frequency and for viability after the expression time; concentration-dependent inhibition of growth both with and without activation. **No adverse effect indicated. Unacceptable**, not upgradeable (single trial only). (Gee, 2/9/90)

** 016 075366 "The Effect of EL-107 on the Induction of Reverse Mutations in Salmonella typhimurium using the Ames Test." (Toxicology Division, Lilly Research Laboratories, Study 841001AMS1378, 10/84) EL-107, Lot Z10025 (mixture of isomers: Compound 121607, 85.0%; 135520, 8.3% and 173490, 2.2%); tested with Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100 with and without Aroclor 1254-induced male rat liver activation; 0 (DMSO), 31, 62.5, 125, 250 or 500 µg/plate; precipitation above 500 µg/plate, confounding colony counting; triplicate plates, single trial; data reported as mean \pm S. D. **No increase in reversion rate. Acceptable.** (Gee, 2/9/90)

** 016 075367 "The Effect of EL-107 (Compound 121607) on the Induction of Reverse Mutations in Salmonella typhimurium and Escherichia coli using the Ames Test." (Toxicology Division, Lilly Research Laboratories, Greenfield, IN, Project nos. 840924AMS1378 and 870615AMS1378A, 9/9/87) EL-107, Lot Z10025 (mixture of isomers: Compound 121607, 85.0%; 135520, 8.3% and 173490, 2.2%); tested with Salmonella typhimurium strains TA1535, TA1537, TA98 and TA100 and with Escherichia coli strain WP2uvrA; with and without Aroclor 1254-induced male rat liver activation, concentrations of 0 (DMSO), 31, 62.5, 125, 250 or 500 µg/plate, triplicate plates, single trial; at 500 µg/plate and above, a precipitate formed interfering with counting of colonies; individual plate counts reported. **No increase in reversion rate. Acceptable.** (Gee, 2/13/90)

** 016 075368 "The Effect of EL-107 (Compound 121607) on the Induction of Reverse Mutations in Escherichia coli Strain WP2uvrA Using the Ames Test." (Toxicology Division, Lilly Research Laboratories, Greenfield, IN, Projects nos. 840924AMS1378 and 870615AMS1378B, 9/9/87) EL-107, Lot Z10025 of EL-107, a mixture of isomers (Compound 121607, 85.0%; 135520, 8.3% and 173490, 2.2%); tested with Escherichia coli strain WP2uvrA trp mutant with and without Aroclor 1254-induced male Fischer 344 rat liver activation; 0 (DMSO), 31, 62.3, 125, 250 or 500 µg/plate, 48 hour incubation, triplicate plates, single trial; precipitation at higher concentrations. **No increase in revertants. Acceptable.** (Gee, 2/13/90)

CHROMOSOME EFFECTS

016 075369 "Mutagenicity Test on EL-107 (Compound 121607); Research for Possible Genotoxic Potential of EL-107 Using the Micronucleus Technique in the Mouse." (Laboratoire d'Histopathologie - CERTI, Paris, for Lilly Research Laboratories, 12/87) EL-107, lot HO2-2G6-118; 85.4% EL-107, 8.8% compound 135520, a structural isomer; 10 male Swiss mice per group, given 0 (peanut oil), 800, 2000 or 5000 mg/kg twice by oral gavage, sacrificed 24 hours after second dosing, benzene as positive control; scored 2000 polychromatic erythrocytes from bone marrow per animal; no scoring of normochromatic erythrocytes; statistically significant increase in percent polychromatic erythrocytes with micronuclei at 800 and 2000 mg/kg; no data on toxicity. **Possible adverse effect indicated. Unacceptable** (males only without justification, single sampling time). Not upgradeable. (Gee, 2/14/90)

016 075370 "The Effect of EL-107 (Compound 121607) on the in vivo Induction of Sister Chromatid Exchange in Bone Marrow of Chinese Hamsters." (Toxicology Division, Lilly Research Laboratories, Greenfield, IN, Project No. 820921SCE1378, 10/82) EL-107, lot HO2-2G6-118; 85.4% EL-107, 8.8% compound 135520, a structural isomer; tested *in vivo* with Chinese hamsters, 2-3 females per group at 0 (10% aqueous acacia), 12.5, 25, 50 or 100 mg/kg body weight; sacrificed after a total of 21 hours; scored 25 second metaphases per female for a total of 75 per dose group; cyclophosphamide as positive control. **No evidence of an adverse effect. Unacceptable** (use of females only without justification, no dose justification with no evidence of toxicity reported.) Not upgradeable. (Gee, 2/15/90)

016 075371 "A Male Effect and Dominant Lethal Study with EL-107 in the Wistar Rat."

(Toxicology Division, Lilly Research Laboratories, Greenfield, IN, Study R01984, 10/85) EL-107, Lot Z10025 of EL-107, a mixture of isomers (Compound 121607, 85.0%; 135520, 8.3% and 173490, 2.2%); fed in the diet to male Wistar rats at 0 (diet), 0.05, 0.25 or 1.25% of the diet for 10 week growth phase; 25 males per group; mated 1:1 with untreated females for 2 weekly periods; females sacrificed on day 20 of gestation and litters assessed; males were from the third generation of treated rats in the 3-generation reproduction study. **No adverse effect indicated** (microphthalmia noted in the reproduction study at 1.25% was not found when males were mated with untreated females). **Unacceptable** (dose justification for a dominant lethal test - same doses were used as in the reproduction study). (Gee, 2/15/90)

016 075372 "Mutagenicity Test on EL-107 (Compound 121607): In an in vitro Cytogenetic Assay Measuring Chromosomal Aberration Frequencies in Chinese Hamster Ovary (CHO) Cells." (Hazleton Laboratories America, MD, HLA Study 9686-0-437, 8/12/87) Isoxaben (EL-107), lot 617AS5, composition not defined; tested with CHO-WBL cells with and without Aroclor 1254-induced rat liver activation; concentrations without activation were 0 (DMSO and negative), 5.01, 10, 20, 40.1 or 80.1 µg/ml, 7.5 hours, with a total of 10 or 20 hours incubation; with activation, tested at 0 (DMSO and negative), 12.5, 25, 50.1, 100 or 200 µg/ml, 2 hours treatment and a total of 10 or 20 hours incubation; duplicate cultures for treatments; scored 100 metaphases per culture for a total of 200 per concentration; scored aberrations and gaps (not included in evaluation of aberrations); preliminary cytotoxicity test to select concentrations used - precipitation at 83.5 µg/ml without activation and at 250 mg/ml with activation. **No increase in chromosomal aberrations. Unacceptable** but upgradeable with submission of analysis of test material lot used in the study. (Gee, 2/20/90)

017 075373 "Mutagenicity Test on EL-107 (Compound 121607): Research for Possible Mutagenic Potentiality of EL-107 Using the Technique of Sister Chromatid Exchanges in the Chinese Hamster." (Laboratoire D'Histopathologie - CERTI, France, Study No. 886 [Histopathology Laboratory, Versailles, France] for Lilly, 12/87 report date of translation, 10/31/84 for original) EL-107, lot Lot H 02-2G6-118 - see Record 075369 for composition [85.4% EL-107, 8.8% compound 135520, a structural isomer; given in a single oral gavage dose at 0 (peanut oil), 800, 2000 or 5000 mg/kg to groups of 10 - 12 male Chinese hamsters; sacrificed 18 hours after dosing and bone marrow prepared for sister chromatid exchange scoring; scored 50 metaphases per animal having satisfactory spreads; dose selection based upon a preliminary test at 5000 and 10,000 mg/kg with no mortality; **no increase in sister chromatid exchanges. Unacceptable** (use of males only was not justified). Possibly upgradeable. (Gee, 2/20/90)

** 017 075375 "Test for Genotoxicity of EL-107 Using a Micronucleus Technique in the Mouse." (CERTI, France, 9/6/84) EL-107, lot HO2-266-118 (?), no purity stated [see 075369]; tested in male Swiss mice at 0 (peanut oil) or 5000 mg/kg by oral gavage given twice at 24 hour intervals; 10/group; sacrificed at 24, 48 or 72 hours after second dosing; positive control of benzene with 24-hour sacrifice; scored 2000 polychromatic erythrocytes per animal. **Increase in incidence of micronuclei at 24 and 48 hour sacrifices. Acceptable** (although only males were used without justification, given the positive results, the study is acceptable.) (Gee, 2/21/90)

DNA DAMAGE

** 017 075374 "The Effect of EL-107 (Compound 121607) on the Induction of DNA Repair Synthesis in Primary Cultures of Adult Rat Hepatocytes." (Toxicology Division, Lilly, Greenfield, IN, Studies 820921UDS1378 and 821026UDS1378, 12/82) EL-107, Lot HO2-2G6-118; See Appendix A for analysis - 85.4% EL-107, 8.8% Compound 135520 - structural isomer; tested with primary rat hepatocytes at 0 (DMSO), 0.05, 0.1, 0.5, 1, 5, 10, 50, 100, 500 or 1000 nmoles/ml, two trials; scored 20 nuclei per concentration; **no evidence of an increase in unscheduled DNA synthesis. Acceptable.** (Gee, 2/21/90)

NEUROTOXICITY

Study type not required at this time.