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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: California Department of Food and Agriculture - EPA Toxicology Review for Trifluralin (TOX CHEM No. 889)

FROM: R. B. Jaeger, Chief 11/27/89
Special Analysis and Outreach Section
Health Effects Division (TS-769C)

TO: William Burnam, Acting Director
Health Effects Division (TS-769C)

The following responses are provided for each specific deficiency identified by the Medical Toxicology Branch of the California Department of Food and Agriculture (CDFA):

STUDY TYPE: Chronic, Dog (Eli Lilly, Study No. D-24-63; 10/66)

Deficiency #1: age and number of animals

EPA Response: EPA concurs that the number of animals is less than is required for long-term dog studies conducted today (3M/3F were used in control and high dose, with 2M/2F in the low dose). Nonetheless, the other two-year dog study conducted using beagles provides additional numbers of dogs, dosed at some of the same dose levels, and via the same route of administration. Concur that the age of the dogs was not reported, however, a reasonable estimate of the age of standard laboratory beagles can be inferred from examination of body weight data.

Deficiency #2: no eye exam or necropsy, incomplete histopathology

EPA Response: EPA concurs with the CDFA deficiencies. These deficiencies have been previously identified by EPA and were partially responsible for classifying this study as Supplementary. Absence of ophthalmoscopic exam has never been a reason on its own merits for downgrading a study. In subsequent long-term dog feeding studies eye exams (histologic) were performed. The other two-year dog study provides additional data regarding necropsy and histopath, also at the same or comparable dose levels.

CONCLUSION: Non-concur with California that subject study is "unacceptable". EPA believes the study provides supplementary data which is supported by data from the two other long-term oral dosing studies in dogs (one in beagles and one in mongrels).

CORE-GRADE: Unchanged (Supplementary).

STUDY TYPE: Chronic, Dog (Eli Lilly, Study No. D 19-62, 10/66)

Deficiency #1: age and number of animals

EPA Response: Concur with CDFA. EPA believes that too few females were used. However, additional data on females as well as males, dosed at the same or comparable dose levels, is available from Eli Lilly Study No. D 24-63. A reasonable estimate of the age of these dogs can be inferred from body weight data in standard laboratory beagles.

Deficiency #2: doses too low

EPA Response: Concur with CDFA. However, there is an overlap of doses and information available in Eli Lilly Study No. D 24-63, demonstrating that 10 mg/kg bwt (the highest dose in Study No. D 19-62) is an NOEL.

Deficiency #3: no eye exam, inadequate histopathology

EPA Response: Concur with CDFA.

CONCLUSION: Non-concur with CDFA that subject study is "unacceptable". EPA believes that subject study provides "supplementary" data which is substantiated by information from two other long-term oral dosing studies in dogs (one in beagles and one in mongrels).

CORE-GRADE: Unchanged (Supplementary).

STUDY TYPE: Chronic, Dog (Eli Lilly, Study No. D 31-61, 10/66)

Deficiency #1: number of animals

EPA Response: Concur with CDFA.

Deficiency #2: no eye exam; inadequate histopathology

EPA Response: Concur with CDFA.

CONCLUSION: Non-concur with CDFA that subject study is "unacceptable". EPA believes the study provides supplementary data when considered in conjunction with the two other long-term oral dosing studies in dogs.

CORE-GRADE: Supplementary.

Overall Remarks: EPA has taken the position that although each individual long-term study conducted in dogs by Elanco has certain recognized deficiencies, they nonetheless provide "supplemental" information on the chronic toxicity in the non-rodent (dog) which is supported by results from dog studies performed separately by Hoechst in 1984. This latter 12-month dog feeding study was provided to EPA by IPiCi in support of their separate registration for Trifluralin. IPiCi also has a complete toxicology data based, which includes two dog studies (a 6-month and a one-year feeding study). These studies were reviewed 4/30/87 with the following conclusions:

6-month subchronic toxicity study in dogs (Study #633, 10/30/81) : LOEL = 400 ppm (lowest dose)
NOEL = not established
CORE-GRADE: Supplementary

Chronic (1 year) feeding study in dogs (Study #A29701, 11/9/84) : LOEL = 150 ppm
NOEL = 30 ppm
CORE-GRADE: Guideline

EPA, therefore, believes that there are sufficient data in the non-rodent (dog) to satisfy the requirement for a long-term study in the dog. No data gap exists. Furthermore, EPA has learned (via telecon 2/?/89) from Elanco that they intend to satisfy the non-rodent data gap to CDFA's satisfaction (e.g. this means they are in negotiations with IPiCi to use their existing dog study performed in 1984 by Hoechst).

STUDY TYPE: Chronic, Dog (Eli Lilly, Study No. D 31-61, 10/66)

Deficiency #1: number of animals

EPA Response: Concur with CDFA.

Deficiency #2: no eye exam; inadequate histopathology

EPA Response: Concur with CDFA.

CONCLUSION: Non-concur with CDFA that subject study is "unacceptable". EPA believes the study provides supplementary data when considered in conjunction with the two other long-term oral dosing studies in dogs.

CORE-GRADE: Supplementary.

Overall Remarks: EPA has taken the position that although each individual long-term study conducted in dogs by Elanco has certain recognized deficiencies, they nonetheless provide "supplemental" information on the chronic toxicity in the non-rodent (dog) which is supported by results from dog studies performed separately by Hoechst in 1984. This latter 12-month dog feeding study was provided to EPA by IPiCi in support of their separate registration for Trifluralin. IPiCi also has a complete toxicology data based, which includes two dog studies (a 6-month and a one-year feeding study). These studies were reviewed 4/30/87 with the following conclusions:

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EPA, therefore, believes that there are sufficient data in the non-rodent (dog) to satisfy the requirement for a long-term study in the dog. No data gap exists.

CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

TRIFLURALIN

SB 950-134, Tolerance # 207

May 27, 1987
Revised October 12, 1988

I. DATA GAP STATUS

Combined rat (chronic + onco.):	No data gap, possible adverse effects.
Chronic dog:	Data gap, inadequate studies, no adverse effects indicated.
Onco mouse:	No data gap , possible adverse effect (not onco).
Repro rat:	No data gap, no adverse effect.
Terato rat:	No data gap, no adverse effect.
Terato rabbit:	No data gap, no adverse effect.
Gene mutation:	No data gap, no adverse effect.
Chromosome:	No data gap, no adverse effect.
DNA damage:	No data gap, no adverse effect.
Neurotox:	Not required at this time.

Note, Toxicology one-liners are attached

** indicates acceptable study
Bold face indicates possible adverse effect
File name T881012
Reviews by J. Christopher, J. Schreider, J. Parker and J. Remsen (Gee)
Toxicology Summary by J. Gee

J. Christopher 11-7-88
J. Gee 11/4/88

COMBINATION, RAT

**002, 003 952930, 952931 "The chronic toxicity of compound 36352 (trifluralin) given as a component of the diet to Fischer 344 rats for two years." (Lilly research, 9/16/80, R-87 and R-97) Trifluralin, 100%, no nitrosamine, lots P-65469 and 326EF8; 60 Fischer 344 Rats/sex/group, 30 in each of two replicate studies; fed at 0, 813, 3250 or 6500 ppm in the diet - dose selection based on NCI study (Record no. 027205); diet analyses at 11 intervals; adverse effects: microcytic anemia (both sexes) at 3250 and 6500 ppm, transitional cell carcinoma of renal pelvis epithelium and bladder (both sexes) and thyroid follicular adenoma and carcinoma (males only); sys NOEL = 813 ppm (decreased body weight gain), chronic NOEL < 813 ppm (progressive glomerulonephroses, renal calculi); Complete; Acceptable. JPC, 5/21/85 and JG, 5/18/87.
No EPA one-liner available. [In the Guidance for the Reregistration of Pesticide Products Containing Trifluralin as the Active Ingredient, August 1986, CDFA Record #51346, Document 207-097, this study is discussed with the footnote that additional data in the Fischer 344 rat is required to resolve the adverse kidney effects "since a NOEL for non-oncogenic kidney effects was not demonstrated...." The EPA states at least one dose should be lower than 813 ppm. JG, 5/14/87.]

094 42832 (Lilly,9/16/80) Historical control data for 002 952930. JPS, 7/24/86.

109 062079, 062080, "A Special Urinalysis Study in Fischer 344 Rats Maintained on Diets Containing Trifluralin (Compound 36352) for Three Months", (Lilly Research Laboratories, study # RO4785, August 1985 and 1986), trifluralin, 96.45% purity, administered in the diet for 3 months to males only with 60/group at 0 and 2.6 mg/kg/day, and with 40/group at 10.7, 42.2, 170.2, and 342.1 mg/kg/day time-weighted average. NOEL for non-oncogenic kidney effects in male Fischer 344 rats = 2.6 mg/kg/day (approx. 50 ppm) (increased urinary K, Ca, AST, LDH, and Alpha 1, Alpha 2 and Beta globulins; increased renal tubular epithelial hyaline droplets). Some were continued on the diets for 4 months followed by 6 weeks on control diet. Treatment effects were reversible in all but the highest dose group. Note: this study was conducted to determine a NOEL for the non-oncogenic kidney effects of trifluralin in the Fischer 344 rat. This question surfaced in the combined rat feeding study record #'s 952930, 952927, and 952931 previously reviewed (JPC, 5/21/85 and JG, 5/18/87, 10/9/88).

CHRONIC, RAT

001 022779, "Chronic toxicity studies with trifluralin." (Eli Lilly, 10/15/63, R31-61), Trifluralin, Lot no. 367-99-0D-223, [98% - see document 207-098]; 5-7 Harlan strain rats/sex/group fed at 0, 20, 200, 2000 or 20,000 ppm trifluralin in the diet; report states NOEL to be 2000 ppm (decreased weight gain, decreased food intake); no adverse effects reported. Unacceptable, not upgradeable (too few animals). JPC, 5/16/85.
EPA one-liner: Systemic NOEL = 2000 ppm; Core grade not stated.

001 022778 "Rat study RO283." (Eli Lilly, 10/66) Trifluralin, lot 367-99-0D-223 [98% - see Document 207-098]; 25 "Cox strain" rats/sex/group fed 0, 200, 1000 or 2000 ppm trifluralin in the diet; increased liver size (both sexes) at 2 years at 2000 ppm (no histopathological findings of significance) but otherwise insufficient information for assessment of adverse effects; NOEL not clear; Unacceptable, not upgradeable - (no MTD for females achieved, inadequate number of survivors at term, no analyses of diet.) JPC, 5/15/85

11/14/88

EPA one-liner: Systemic NOEL greater than 2000 ppm; Core grade not stated.

087 036893 More complete version of 22778.

010 952925 Very brief summary (abstract); not SB 950 data (occupational hazards).

038 952919 Summary; duplicate information to 001 022779.

044 952920 Summary; duplicate information to 001 022779.

053 022874 Very brief summary; duplicate information to 001 022779.

087 036892 Duplicate information to 001 022779 (incomplete report).

CHRONIC, DOG

→ 010 022879 "Study D24-63." (Eli Lilly Co., 10/66) Trifluralin (98% from Document 207-098), lot no. 367-99-0D-223; given by oral capsule, three years; 0, 10, or 25 mg/kg (stated as equivalent to 400 and 1000 ppm in the diet), 2-3/sex/group; monthly blood and urine sample analyses; NOEL = 10 mg/kg for increased liver weight but no pathology reported; **unacceptable** (age and number of animals, no eye exam or necropsy, incomplete histopathology, breeding of females); not upgradeable; **no adverse effect** identified. Females were bred to a male in the same dose group in the third year - see #022873. JPC, 5/14/85, JPS, 7/25/86 and FM, 5/22/87.
EPA one-liner: Systemic NOEL = 10 mg/kg; Core grade not stated.

93 42586 Supplement to 022879; contains duplicate text and tables;contains some necropsy sheets and a photograph and description. JPS, 7/25/86.

044 952920 Incomplete report; duplicate information to 010 022879.

053 022882 Very brief summary; Duplicate information to 010 022879.

→ 010 022880 "Study D19-62." (Eli Lilly Co., 10/66) Summary only. Trifluralin, (98% from Document 207-098), lot no. 367-99-0D-223; two-year study by daily capsule, 1/sex in controls and 2.5 mg/kg, 2/sex at 1 mg/kg, 2 males only at 5 and 10 mg/kg - stated to be equivalent to 40, 100, 200 and 400 ppm in the diet; beagle dogs, "various" ages; **unacceptable** (age and number of animals, several females bred, doses too low, no eye exam, inadequate histopathology) with **no adverse effect** reported. JPC, 5/14/85, JPS, 7/25/86 and FM, 5/22/87.

093 42585 Exact duplicate of first 11 pages of 010 022880. JPS, 7/25/86

→ 010 022881 "Study D31-61." (Eli Lilly Co., 10/66) Summary with data; Trifluralin, (98% from Document 207-098), lot no. 367-99-0D-223; dose levels were 0, 2.5, 5.0, 10.0, or 25.0 mg/kg (equivalent to 100, 200, 400 and 1000 ppm in a diet) given in capsules administered daily for 730 days; one male and female mongrel dog were in each group except the 10.0 mg/kg group (2 females); **no adverse effects** reported; **unacceptable** (number of animals, breeding of one female, no eye exam, inadequate histopathology, otners.) JPC, 5/14/85, JPS, 7/25/86 and FM, 5/22/87.
EPA one-liner: Systemic NOEL = 25 mg/kg; Core grade not stated.

010 022871 & 022872 Summary, no data (Trifluralin residues, dog fat samples--study not identified.

[In the Guidance for the Reregistration of Pesticide Products Containing Trifluralin as the Active Ingredient, April, 1987, the EPA considers sufficient data are contained in the 1966 report(s) for studies in dogs. The conclusions of CDFA, however, disagree that the three studies collectively provide sufficient data for regulatory purposes. JG, 5/14/87 and F. Martz, 5/22/87.]

ONCOGENICITY, RAT

001 027205 "Bioassay of trifluralin for possible carcinogenicity." (Hazleton Laboratories, for NCI, 1978, Report No. (NIH) 78-834) Trifluralin, technical grade, > 90% with 13 impurities including 84 to 88 ppm dipropylnitrosamine; fed in the diet at 0, 4125 (males and females) or 8000 ppm (males), 7917 ppm (females), time-weighted averages - initial dose levels were 6500 and 13,000 ppm, reduced to 3250 and 6500 at week 21 and schedule changed to 1 week off test material and 4 weeks on test diet at week 41 or 46 for the high dose groups; 50/sex/group; 18 months followed by 33 weeks on control diet; **no adverse effects** reported; apparent systemic NOEL < low dose (body weight gain in males and females throughout study), onco NOEL > high dose; no histopathological findings reported; **unacceptable**--major variances (no analyses of diet, length of 18 months only on test material, housing of multiple studies in one animal room, change in dose levels during study, not all high dose animals examined histopathologically, no individual data); Not upgradeable. JPC, 5/15/85 and JR(G), 12/2/85.
EPA one-liner: Systemic NOEL = 3250 ppm; Oncogenic NOEL greater than 6500 ppm; Core grade not stated. Presence of nitrosamine makes results equivocal.

085 038382 (Hazleton/NCI, 1978) Supplemental information for 001 027205 (Review by data evaluation/risk assessment subgroup, Clearinghouse on environmental carcinogens--also contains individual histopathology). JPC, 12/2/85.

085 036889 Partial duplicate of 001 027205, 027206.

002 952936 Summary; duplicate information to 001 027205, 027206.

ONCOGENICITY, MOUSE

001 027206 "Bioassay of trifluralin for possible carcinogenicity." (Hazleton Laboratories for NCI, 1978, Report no. (NIH) 78-834) Trifluralin, technical grade (greater than 90% purity with 13 impurities including 84 to 88 ppm dipropylnitrosamine; time-weighted average doses of 2000 or 3744 ppm (males) and 2740 or 5192 ppm (females); dose levels were 9000 and 4500 at start but lowered after 17 weeks; 20/sex (control) and 50/sex/test group; systemic NOEL < low dose in females (decreased body weight gain); **unacceptable** - many problems with inadequate number of control animals, housing of animals on several studies in the same room, histopathology on only some survivors - not all, no analyses of diets, no individual data.) Although "summary" identifies **adverse effects** of increased incidence of hepatocellular carcinomas and alveolar/bronchiolar adenomas in females, these are difficult to interpret in view of study shortcomings. Record # 038383, contains the individual histopathology data in addition to the report. Also, part of the document is a discussion of the content of dipropylnitrosamine in the lot of trifluralin used by Hazleton for the study and attributes the oncogenicity to this impurity. For this reason, the positive results in this study are suspect. Subsequently, new studies were initiated by Lilly in which there was no detectable level of DPNA. JPC, 5/15/85 and JR(G), 12/2/85 (see 038383)

EPA one-liner: Systemic NOEL less than 2000 ppm (bodyweight depression); Oncogenic NOEL less than 2250 ppm (LDT; average concentration; increased incidence of hepatocellular adenoma or carcinoma, alveolar-bronchiolar adenoma, and squamous-cell carcinoma in female mice). Core grade not stated.

085 038383 Supplement to 27206; individual data plus commentaries.

085 036888 Partial duplicate of 001 027205, 027206.

073 022885 Partial duplicate of 001 027205, 027206.

** 004, 005 952928, 952929 "The chronic toxicity of compound 36352 (trifluralin) given as a component of the diet to the B6C3F1 mouse for 24 months." (Lilly Research Lab, 9/16/80, Studies M-9067 and M-9077) Trifluralin technical, 99.8%, with no detectable dipropylnitrosamine to 0.01 ppm sensitivity, lot nos P-65469 and 326EF8; 120/sex in control and 80 B6C3F1 mice/sex/test group (2 replicate studies); fed 0, 563, 2250 or 4500 ppm in the diet; **adverse effects** of anemia and altered kidney function at mid- and high-doses; sys NOEL = 563 ppm (decreased body weight and altered relative organ weights of liver, kidney, hepatocellular hypertrophy and hyperplasia), oncogenic NOEL > 4500 ppm; Complete and **Acceptable.** JPC, 5/16/85
EPA one-liner: No further data required - considered adequate for regulatory purposes with no oncogenic effects.

REPRODUCTION, RAT

089 036912 Summary only; see one-liner under "Teratology, Rat"

010 022878 "Breeding Studies, Rats." (Elanco, 10/66) Trifluralin, (98% from Document 207-098), lot 367-99-0D-223; 3 generations, 2 litters; 0, 200 or 2000 ppm in the diet; 6 males/group, 12 females/group; **insufficient information for adverse effect assessment; unacceptable** with major variances (only 2 dose levels, insufficient number of animals, no analyses of diet presented, others.) JPC, 5/15/85

EPA one-liner: Reproductive NOEL = 200 ppm, Core grade = Supplementary.

010 022875 Supplement to 010 022878 (very brief summary of litter data).

952877 Very brief interim report, 4/25/63; Supplemental information to 010 022878.

044 952943 Summary; duplicate information. to 010 022878.

053 022882 Very brief summary; Duplicate information. to 010 022878

089 036911 Brief interim report; Supplemental to 010 022878.

** 099, 100, 101 50750, 50751, 50752 "A One-year Two-generation Reproduction Study in CD Rats Maintained on Diets Containing Trifluralin." (Lilly Research Labs, 8/86, R06384 and R13984) Trifluralin technical, 96.45%, lot 554AP2, initial nitrosamine content at 0.33 ppm with 99.43% off contents identified; fed in the diet at 0, 0.02, 0.63 or 0.2% (equivalent to TWA's of 15, 47 and 148 mg/kg/day); 25/sex/group; 2 litters per generation; parental NOEL = 0.063% (decreased body weight gain), reproductive NOEL > 0.2%; **no adverse reproductive effect reported; acceptable.** JG, 5/14/87.

REPRODUCTION, DOG

010 022873 "Breeding Study, Dogs." (Elanco, no date) Trifluralin (no purity stated), lot 367-99-0D-223; 0, 10, or 25 mg/kg; bred in third year; part of 3 year chronic study (see 010 022879); **insufficient information for adverse effects assessment; unacceptable** with major variances for reproduction study; not upgradeable. JPC, 5/15/85.
EPA one-liner: Reproductive NOEL = 25 mg/kg; Core grade not stated.

010 022876 Part of 010 022873 (very brief summary of litter data).

TERATOGENICITY, RAT

** 089 036914 "A Teratology Study of Trifluralin (EL-152, Compound 36352) Administered Orally to Charles River CD Rats." (Lilly Research Laboratories, 10/22/84, Study R08484) Trifluralin (96.7% pure), lot 00554AP2; given by oral gavage at 0, 100, 225, 475 or 1000 mg/kg, 25 rats/group; NOEL(maternal toxicity) = 225 mg/kg/day (decreased body weight and food consumption); NOEL (developmental toxicity) = 475 mg/kg/day (decreased fetal weight); **acceptable. No adverse developmental toxicity** reported. JAP, 12/6/85.
EPA one-liner: Teratogenic NOEL > 100 mg/kg/day, maternal NOEL = 225 mg/kg/day (decreased body weight and lowered food consumption); fetotoxic NOEL = 475 mg/kg/day (decreased mean fetal weight); Core grade = Minimum.

089 036917 "Review of Rat and Rabbit Teratology Studies of Trifluralin (EL-152) (Lilly Research Lab. 1/85) Supplemental information. for 089 036914 (Review by Argus Intl., Inc.; 1/4/85). JAP, 12/6/85.

089 036912 "A Study of the Effects of Trifluralin on Pregnant Rats and Their Progeny." (Lilly Research Lab., Study R-1265, no date): Summary (3 pages) prepared by I. Mauer of EPA; Trifluralin (lot #X-26920, unstated purity, contaminants not given) fed at 0, 0.05%, 0.1%, 0.2% (0, 500, 1000, 200 ppm) 30/group; 10 fed throughout gestation and lactation and allowed to deliver; offspring fed on test diet until 3 months; this submission consists of EPA memorandum reviewing teratology component only; **no adverse effects** cited. The full study does not appear to be on file at CDFA.
EPA one-liner: Core supplementary (no analyses of diet, no NOEL established - doses too low, no maternal clinical effects, test compound not characterized, others.)

TERATOGENICITY, RABBIT

** 089 036915 "A Teratology Study (I) of Trifluralin (EL-152, Compound 36352) Administered Orally to Dutch Belted Rabbits." (Lilly Research Labs., 10/31/84, Study B02283 and Study B01784) Trifluralin (96.7% pure), lot 00554AP2; 0, 100, 225, 500, or 800; oral gavage, days 6 - 18; 20/group; maternal NOEL = 225 mg/kg (maternal death and abortions), developmental toxicity NOEL = 225 mg/kg (decreased fetal weight); Complete and **acceptable with 036916. No adverse developmental toxicity** reported. JAP, 11/18/85.
EPA one-liner: Maternal NOEL = 225 mg/kg (abortions and anorexia), fetotoxic NOEL = 225 mg/kg (decreased percentage of live fetuses - cardiomegally and wavy ribs at 500 mg/kg/day); Core grade = Supplementary

089 036908 & 036909 Revised protocol; Supplemental to 089 036915.

089 036910 Brief interim report for 089 036915

11/14/85
11-7-88

089 036918 "Review of Rat and Rabbit Teratology Studies of Trifluralin (EL-152) (Lilly Research Lab, 1/85) Review by Argus Intl., Inc. 1/4/85; Supplemental to 089 036915. JAP, 12/6/85.

** 089 036916 "A Teratology Study (II) of Trifluralin (EL-125, Compound 36352) Administered to Dutch Belted Rabbits." (Lilly Research Lab.s, 12/6/85, Study B01784) Trifluralin (96.7%) given by oral gavage at 0, 100, 225, 500 mg/kg; 25/group; **no adverse effects** reported; maternal NOEL = 100 mg/kg (death, abortions, decreased body weight gain, food consumption); developmental toxicity NOEL = 225 mg/kg (decreased fetal weight, increased resorptions); complete and **acceptable with 089 036915.** JAP, 10/31/85.
EPA one-liner: Maternal NOEL = 100 mg/kg/day, fetotoxic NOEL = 225 mg/kg/day; Core grade = Minimum.

010 022877 "Rabbit Study B9-65." (Elanco, 10/66) Trifluralin (no purity stated); 0, 225, 450, or 1000 mg/kg by oral gavage, days 8 through 16; 8/group; **insufficient information for adverse effects assessment; unacceptable** (no purity stated, no analyses of dosing solutions, inadequate number of animals, no data on fetal findings, others). JPC, 5/15/85.
EPA one-liner: Teratogenic NOEL = 450 mg/kg, reproductive NOEL = 450 mg/kg; Core grade = Supplementary

MUTAGENICITY, GENE MUTATION

Bacterial systems

088 036899 & 036894 "The Effect of Trifluralin (Compound 36352) on the Induction of Reverse Mutations in Salmonella typhimurium using the Ames Test." (Lilly Research Laboratories, 3/24/83) Trifluralin (95%); Salmonella strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100 tested with (0-800 ug/plate) and without (0-400 ug/plate) rat liver activation, limited by solubility; **no increase in revertants;** triplicate plates, single trial; **Unacceptable** (no confirming repeat trial.) JR(G), 11/26/85.
EPA one-liner not available.

Mammalian systems

088 036896 & 036900 "The Effects of Trifluralin (Compound 36352) on the Induction of Forward Mutation at the Thymidine Kinase Locus of L5178Y Mouse Lymphoma Cells. (Lilly Research Labs., 3/24/83) Trifluralin, 95%, lot 00554AP2; tested at 0, 0.5, 1.0, 2.5, 5.0, 7.5, 10, 15 or 20 ug/ml, incubated for 4 hours; **no increase in M.F.** reported; no confirming experiment; **unacceptable** (no confirming experiment.) JR(G), 4/26/85,
EPA one-liner not available.

Summary: While neither study was found acceptable due to flaws in the design or in reporting of the data, CDFA believes collectively the two provide sufficient data to determine that there is not a mutagenic effect.

MUTAGENICITY, CHROMOSOMAL ABERRATION

** 088 036902, 036898, 036903, "A Dominant Lethal Study with Technical Trifluralin (Compound 36352) in the Wistar Rat.", (Lilly Research Lab., 6/23/83), Trifluralin (95%), 15 males/group were given 0, 0.1 or 1 g/kg/day by gavage for 5 days followed by mating 1:1 with females for 7 days, 10 weeks;

TEM as positive control; **no adverse effect** on reproduction or fertility reported; initially reviewed as unacceptable based on an insufficient number of pregnant females per time interval. Reconsideration of the total data available for the compound including genotoxicity and long-term animals studies, this study has been upgraded to **acceptable.** JR(G), 11/27/85 and 5/15/87.
EPA one-liner not available. According to the reregistration standard for trifluralin, no further data are required.

MUTAGENICITY, DNA/OTHER

** 088 036901, 036897 "The Effect of Trifluralin (Compound 36352) on the in vivo Induction of Sister Chromatid Exchanges in Bone Marrow of Chinese Hamsters." (Lilly Research Laboratories, 3/24/83) Trifluralin (95%) for Elanco, female Chinese hamsters given 0, 200, 300, 400 or 500 mg/kg in single gavage dose; 2-3 per group; sacrificed and scored 21 hour later with 25 metaphases scored in second division for SCE's; number/100 metaphases in first, second or third division; cyclophosphamide controls; initially reviewed as unacceptable with major variances based on use of only females, and the low number of animals. Considering the total data base for the compound, the fact that evidence is presented for exposure of the marrow in terms of a dose-dependent increase in the number of cells in M1 at 21 hours and the fact that there was **no indication in the presence of this change of an increase in SCE's,** the study was upgraded to **acceptable** with variances. JR(G), 11/27/85 and 5/15/87
EPA one-liner not available. According to the reregistration standard for trifluralin, no further data are required.

088 036895 Protocol; part of information. to 088 036901.

NEUROTOXICITY

Not required at this time.

11/14/88
11-7-88

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