5

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361
UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUL 27 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Subject: Toxicology Review for the Reregistration Eligibility Document on Ethalfluralin

To: Flora Chow, Head, Reregistration Section
Chemical Coordination Branch
Health Effects Division (7509C)

From: Patricia McLaughlin, Ph.D. P M^c Laughlin 7/21/94
Toxicology II Branch, HED (7509C)

Thru: Clark Swentzel, Head, Section II R. Clark Swentzel 7/21/94
Toxicology II Branch, HED (7509C)

Marcia van Gemert, Ph.D., Chief Marcia van Gemert 7/27/94
Toxicology II Branch, HED (7509C)

Chemical: Ethalfluralin, or EL-161, or Sonalin, or N-ethyl-N-(2-methyl-2-propenyl)-2,6-dinitro-4-trifluoromethyl)benzenamine

Case 2260; chemical 113101; CAS Reg No. 55283-68-6

S459915, D200166

Products: preemergence herbicide for terrestrial food uses
Partial package received 3/11/94

NOTE: The Carcinogenicity Peer Review is not final and this information should be completed before this chapter leaves HED.

MEMORANDUM

Subject: Toxicology Review for the Reregistration Eligibility Document on Ethalfluralin

To: Flora Chow, Head, Reregistration Section
Chemical Coordination Branch
Health Effects Division (7509C)

From: Patricia McLaughlin, Ph.D.
Toxicology II Branch, HED (7509C)

Thru: Clark Swentzel, Head, Section II
Toxicology II Branch, HED (7509C)

Marcia van Gemert, Ph.D., Chief
Toxicology II Branch, HED (7509C)

Chemical: Ethalfluralin, or EL-161, or Sonalin, or N-ethyl-N-(2-methyl-2-propenyl)-2,6-dinitro-4-trifluoromethyl)benzenamine

Case 2260; chemical 113101; CAS Reg No. 55283-68-6

S459915, D200166

Products: preemergence herbicide for terrestrial food uses
Partial package received 3/11/94

NOTE: The Carcinogenicity Peer Review is not final and this information should be completed before this chapter leaves HED.

1. Toxicology Data Base

The toxicological data base on ethalfluralin is adequate and will support reregistration eligibility.

a. Acute Toxicity

ACUTE TOXICITY DATA

TEST	RESULTS	CATEGORY
Oral LD_{50}--rat	LD_{50} >5000 mg/kg	IV
Dermal LD_{50}--rabbit	LD_{50} >5000 mg/kg	IV
Inhalation LC_{50}--rat	LC50 >0.94 mg/L	III
Eye irritation--rabbit	moderate	II
Dermal irritation--rabbit	moderate to severe	II
Skin sensitization--guinea pig	sensitizer	---

An acute oral toxicity study with rats found the LD_{50} was greater than 5000 mg/kg, which was toxicity category IV (guideline 81-1; MRID 41613908). An acute dermal toxicity study with rabbits found the LD_{50} was greater than 5000 mg/kg. This was toxicity category IV (guideline 81-2; MRID 41613909).

An acute inhalation study with rats found the LC_{50} was greater than 0.94 mg/L, which was toxicity category III (guideline 81-3; MRID 41977601).

An eye irritation study with rabbits found slight to moderate corneal opacity and edema with slight to severe iritis and irritation up to the third day, generally followed by clearing by the seventh day. One animal retained scattered opacity through day 7, clearing by day 14. This was toxicity category II (guideline 81-4; MRID 41613910). A dermal irritation study with rabbits found slight to moderate irritation and edema from 24 hours through 7 days after 24 hour dermal treatment. There were desquamation, slight to severe edema and irritation, with coriaceous formation,

through 14 days. One animal had epidermal fissures and bleeding by the fourteenth day. This was toxicity category II (guideline 81-5; MRID 41613909).

A guinea pig dermal sensitization study conducted by the modified Buehler method found no sensitization, whereas a study conducted by the Magnusson and Kligman maximization method found ethalfluralin was positive (guideline 81-6; MRID 00070683a).

b. Subchronic Toxicity

A three month feeding study with B6C3F1 mice used doses of 0, 560, 1110, 2250, 4000, and 8000 ppm (68, 136, 285, 538, and 1205 mg/kg/day). The NOEL was 560 ppm. The LOEL was 1110 ppm based on low bilirubin and low kidney weights in males. Higher doses showed depressed weight gain, increased SGPT, increased serum alkaline phosphatase, and increased relative liver weights. (guideline 82-1; MRID 00070678a)

Ethalfluralin was administered to B6C3F1 mice for one year at dietary concentrations of 0, 100, 400, and 1500 ppm (equivalent to 0, 12, 47.0, and 173 mg/kg/day for males; 0, 12, 49, and 184 mg/kg/day for females). The NOEL was 100 ppm. The LOEL +was 400 ppm, based on increased alkaline phosphatase levels at this and the high dose. At the high dose, there were decreased BUN and creatinine, increased SGPT, and increased relative liver weights. (adequate for a subchronic study, guideline 82-1; MRID 00070679)

Ethalfluralin was fed to Fisher 344 rats for one year. The doses were 0, 100, 250, and 750 ppm in the diet (equivalent to 0, 3.9, 9.7, and 28.4 mg/kg/day for males; 0, 4.9, 11.9, and 34.4 mg/kg/day for females). The NOEL was 100 ppm. The LOEL was 250 ppm, based on blood chemistry changes at the two higher doses, with

increased relative liver weights and decreased body weight gain at the high dose. (This study fills guideline 82-1; MRID 00070678b)

The doses for the preceding study, and for the two year rat study discussed below, were derived from a three month study in which Fischer 344 rats were fed 0, 250, 500, 1100, 2500, or 5000 ppm test material. The NOEL was 500 ppm (29 mg/kg/day). Higher doses showed increased liver and kidney weights, lower RBC, hematocrit and hemoglobin, as well as some enzyme activity changes (MRID 00097327a).

A three month oral study with beagle dogs gave doses of 0, 6.25, 27.5, or 125/80 mg/kg/day by capsule. The systemic NOEL was 27.5 mg/kg/day. The systemic LOEL was 80 mg/kg/day (the high dose) based on elevated alkaline phosphatase, slight fatty metamorphosis of the liver, increased cholesterol, and increased BUN. (guideline 82-1; MRID 00097327b)

In a 21 day dermal toxicity study, New Zealand white rabbits were treated with 0 or 1000 mg/kg/day, a limit dose. No systemic effects were found at this dose; skin effects were slight to severe dermal irritation, as well as edema and coriaceous skin with epidermal fissures. (guideline 82-2; MRID 00257855)

c. Chronic Toxicity and Carcinogenicity

Ethalfluralin was administered to Fisher 344 rats in the diet for two years in combined chronic toxicity and carcinogenicity replicate studies. The doses were 0, 0.01, 0.025, and 0.075 percent in the diet (equivalent to 0, 4.2, 10.7, and 32.3 mg/kg/day). The NOEL for systemic effects was 32.3 mg/kg/day, the high dose. Mammary gland fibroadenomas were found in dosed female rats. (guidelines 83-1, 83-2; MRID 00070678c)

Ethalfluralin was administered to B6C3F1 mice in the diet for two years in combined chronic toxicity and carcinogenicity replicate studies. The doses were 0, 100, 400, and 1500 ppm in the diet (equivalent to 0, 10.3, 41.9, and 163.3 mg/kg/day). No increased incidence of neoplasms was attributed to the treatment. The NOEL was 10.3 mg/kg/day. The mid dose (LOEL) and high dose showed focal hepatocellular hyperplasia in both sexes. There were increased relative liver, kidney, and heart weights in females. Some blood changes were found also, including decreased hematocrit, hemoglobin, and erythrocyte count accompanied by increased mean corpuscular hemoglobin concentration in high dose females. Alkaline phosphatase values were increased at the high dose in both sexes. Body weight gain decreased at the high dose (guidelines 83-1, 83-2; MRID 00070680)

Beagle dogs were given 0, 4, 20, or 80 mg/kg/day orally, by capsule, for one year. The NOEL was 4 mg/kg/day. The LOEL was 20 mg/kg/day, based on increased urinary bilirubin, variations in erythrocyte morphology, increased thrombocyte count, and increased erythroid series of the bone marrow. Elevated alkaline phosphatase levels were found at the two higher doses and siderosis of the liver at the high dose (guideline 83-1; MRID 00260434a)

d. Developmental Toxicity

Ethalfluralin was administered orally to Sprague Dawley rats at 0, 50, 250, or 1000 mg/kg/day on gestation days 6-15. The maternal NOEL was 50 mg/kg/day. The maternal LOEL was 250 mg/kg/day, based on decreased body weight gain and dark urine. The developmental NOEL was 1000 mg/kg/day, the highest dose. (guideline 83-3; MRID 00260434b)

Dutch Belted rabbits were given 0, 25, 75, 150, or 300 mg/kg/day of ethalfluralin by gavage on gestation days 6-18. The NOELs for maternal and developmental toxicity were 75 mg/kg/day. The maternal LOEL at 150 mg/kg/day was based on abortions and decreased food consumption. These effects as well as decreased weight gain, enlarged liver, and orange urine were found at 300 mg/kg/day. The developmental LOEL was 150 mg/kg/day, based on slightly increased resorptions, abnormal cranial development, and increased sternal variants. (guideline 83-3; MRID 00250596)

e. Reproduction

A three-generation reproduction study in Fischer 344 rats gave doses of 0, 100, 250, and 750 ppm in the diet (equivalent to 0, 5.0, 12.5, and 37.5 mg/kg/day). The parental NOEL was 12.5 mg/kg/day. The parental LOEL was 37.5 mg/kg/day, based on depressed mean body weight gains in males in all generations. No treatment-related effects were noted on reproductive parameters and the NOEL was 37.5 mg/kg/day or greater. (MRID 00094784; 00070682)

A seven month multigeneration bridging study was conducted with doses of 0, 100, 250, and 750 ppm (equivalent to 0, 8, 20, and 61 mg/kg/day) in the diet of Fischer 344 rats. The parental NOEL was 20 mg/kg/day. The parental LOEL was 61 mg/kg/day, based on increased liver weights. No treatment-related effects were noted on reproductive parameters and the reproductive NOEL was equal to or greater than 61 mg/kg/day (MRID 42300301). (These two studies combined fill guideline 83-4.)

f. Mutagenicity

Ethalfluralin was weakly mutagenic in activated strains TA1535 and TA100 of Salmonella typhimurium but not in strains TA1537, TA1538, and TA98 in an Ames assay. In a modified Ames assay with

Salmonella typhimurium and Escherichia coli, ethalfluralin was weakly mutagenic in strains TA1535 and TA100, with and without activation, and in strain TA 98 without activation, at the highest dose. No mutagenicity was found in the mouse lymphoma assay for forward mutation. Ethalfluralin did not induce unscheduled DNA synthesis in rat hepatocytes. (MRID 00250475a-d) In Chinese hamster ovary cells, the chemical was negative without S9 activation, but it was clastogenic with activation (MRID 00259342). (These studies fill guidelines 84.)

g. Metabolism

Fischer 344 rats were treated orally with a single low dose, a single high dose, or repeated low doses. Absorption of ethalfluralin was estimated at 79-87% of the dose. Ethalfluralin was rapidly and extensively metabolized, and 95% of the chemical was excreted in urine and feces by seven days. The major route of elimination for the radiolabel was in the feces, 50.9-63.2%, and the levels remaining in the tissues after 72 hours were negligible. The major metabolites in urine and feces were identified. (guideline 85-1; MRIDs 00070683b; 42822901)

A study with Rhesus monkeys indicated that 2.8% of a dermal dose was absorbed through the skin (MRID 00072180).

h. Reference Dose (RfD) for Chronic Oral Exposure

The RfD was determined to be 0.04 mg/kg/day, based on a NOEL of 4.0 mg/kg/day in a one-year oral dog study. An uncertainty factor of 100 was used to account for inter-species extrapolation and intra-species variability.

REFERENCES

00070678a Adams, E.R.; Gossett, F.O.; Hoffman, D.G.; Owen, N.V.; Emmerson, J.L.; Morton, D.M. 1978. Three Month Oral Toxicity Study of Ethalfluralin (94961; EL-161) in Mice. Study No. M-9286. Unpublished study conducted by Lilly. (also 00094774)

00070678b Adams, E.R.; Owen, N.V.; Hoffman, D.G. 1979. A One-Year Dietary Toxicity Study with Ethalfluralin (Compound 94961) in the Fisher 344 Rat. Study No. R-257. Unpublished study conducted by Lilly. (also 00094775)

00070678c Adams, E.R.; Owen, N.V.; Emmerson, J.L. 1981. Two-Year Dietary Evaluation of Ethalfluralin in the Fisher 344 Rat. Study Nos. R-267, R-277. Unpublished study conducted by Lilly. (also 00094776, 92062013)

00070679 Adams, E.R.; Owen, N.V.; Emmerson, J.L. 1981. A One-Year Dietary Toxicity Study with Ethalfluralin (Compound 94961) in the B6C3F1 Mouse. Study No. M-9157. Unpublished study conducted by Lilly. (also 00094777)

00070680 Adams, E.R. 1981. A Two-Year Dietary Evaluation of Ethalfluralin (Compound 94961) in the B6C3F1 Mouse. Study Nos. M-9167, M-9177. Unpublished study conducted by Lilly. (also 00094778)

00070683a Adams, E.R.; Pierson, C.L.; Arthur, B.H. 1981. Guinea Pig Sensitization Studies of Ethalfluralin. Study Nos. G-9530, G-00379. Unpublished studies conducted by Lilly.

00070683b Adams, E.R.; Hanasono, G.K.; Hoffman, D. 1981. Metabolism and Disposition of Ethalfluralin in Male Wistar Rats. No study number. Unpublished study conducted by Lilly. (also 00094789)

00072180 Adams, E.R.; Bridge, T.L.; Van Lier, R.B.L. 1982. Percutaneous Absorption of 14C-Ethalfluralin in Monkeys. Study Nos. M-6162, PO-3282. Unpublished study conducted by Lilly. (also 00132820)

00094784 Adams, E.R.; Owen, N.V.; Emmerson, J.L. 1981. A Multi-Generation Reproduction Study with Ethalfluralin (Compound 94961) in the Fischer 344 Rat. Study Nos R-68, R-738, R-1248. Unpublished study conducted by Lilly. (also 070682)

00097327a Adams, E.; Gossett, F.; Hoffman, D; et al. 1978. Three-Month Oral Toxicity Study of Ethalfluralin (94961, EL-161) in Rats. Study No. R936. Unpublished study submitted by Lilly.

00097327b Gossett, F.; Koenig, G.; Harris, P. 1974. Subacute Toxicity of EL-161 ... Technical Grade in Dogs. Study No. D3733. Unpublished study submitted by Lilly. (also 00135193)

00250475a Thompson, C.; Adams, E.; Probst, G. 1983. The Effect of Ethalfluralin on the Induction of Bacterial Mutation Using a Modification of the Ames Test. Study No. 830404GPA1169. Unpublished study submitted by Lilly. (also 00128693)

00250475b Rexroat, M.; Adams, E.; Probst, G. 1983. The Effect of Ethalfluralin (Compound 94961) on the Induction of Reverse Mutations in Salmonella typhimurium Using the Ames Test. Studies 830307-, 830404-, 830425-AMS1169. Unpublished studies submitted by Lilly.

00250475c Oberly, T.; Bewsey, B.; Adams, E. 1983. The Effect of Ethalfluralin (Compound 94961) on the Induction of Forward Mutation at the Thymidine Kinase Locus of L5178Y Mouse Lymphoma Cells. Study 830208MLA1169. Unpublished study submitted by Lilly. (also 00128696)

00250475d Probst, G.S.; Neal, S.B.; Adams, E.R. 1980. The Effect of Ethalfluralin (Lilly Compound 94961) on the Induction of DNA Repair Synthesis in Primary Cultures of Adult Rat Hepatocytes. Study No. 791120-263. Unpublished study conducted by Lilly. (also 0070682, 00094786)

00250596 Byrd, R.; Adams, E.R.; Fisher, L.F.; et al. 1983. A Teratology Study of Ethalfluralin Administered Orally to Butch Belted Rabbits. Study No. B01383. Unpublished study conducted by Lilly. (also 00129057)

00257855 Brown, G. 1985. Subchronic (21-day) Dermal Toxicity Study in New Zealand White Rabbits with Technical Ethalfluralin. Study No. B01384. Unpublished study conducted by Lilly. (also 00145767)

00259342 Mosesso, P.; Dean, B.; Forster, R. 1985. Test Substance: Ethalfluralin. Chromosome Aberrations in Chinese Hamster Ovary Cells (CHO) In Vitro. Study No. 095003M02385. Unpublished study prepared by Life Science Research Roma. (also 00152219)

00260434a Adams, E.; Bernhard, N. 1985. The Toxicity of Ethalfluralin Administered Orally to Beagle Dogs for One Year. Study No. DO 1684. Unpublished study conducted by Lilly. (also 00262711, 00153371, 92062014)

00260434b Robinson, K. it al. 1985. A Teratology Study of Orally Administered Ethalfluralin (EL-161) in the Rat. Study No. 82182. Unpublished study conducted by Bioresearch Labs. (also 00153370, 92062017)

41613908 Adams, E.R.; Gardner, J.B.; Sites, D.L. 1990. The Acute Toxicity of Ethalfluralin (EL-161, Compound 094961) Administered Orally to the Fischer 344 Rat. Study No. B09490. Unpublished study conducted by Lilly.

41613909 Adams, E.R.; Rock, G.L.; St. Clair, R.L. 1990. The Acute Dermal Toxicity and Primary Dermal Irritation of Ethalfluralin (EL-161, Compound 094961) in the New

Zealand White Rabbit. Study No. B01390. Unpublished study conducted by Lilly.

41613910 Adams, E.R.; Rock, G.L.; St. Clair, R.L. 1990. The Acute Ocular Irritation of Ethalfluralin (EL-161, Compound 094961) in the New Zealand White Rabbit. Study No. B01490. Unpublished study conducted by Lilly.

41977601 Wolff, R.K.; Allen, D.L.; Williams, G.D.; Adams, E.R. 1991. The Acute Inhalation Toxicity in the Fischer 344 Rat of Technical Ethalfluralin. Study No. R17191. Unpublished study conducted by Lilly.

42300301 Hoyt, J.A.; Owen, N.V.; Adams, E.R. 1992. A 7-Month Multigeneration Bridging Study of Ethalfluralin (EL-161, Compound 094061) Administered in the Diet to Fischer 344 Rats. Study Nos. R16890, R16990. Unpublished study conducted by Lilly.

42822901 Eschbach, J.C.; Hackett, D. 1993. Absorption, Distribution, and Elimination of 14C-Ethalfluralin in Rats. Study No. DR-0233-3655-001. Unpublished study conducted by Bio/dynamics.

13544

056548

Chemical:	**Ethalfluralin**
PC Code:	**113101**
HED File Code	**13000 Tox Reviews**
Memo Date:	**07/27/94**
File ID:	**DPD200166**
Accession Number:	**412-03-0019**

HED Records Reference Center
01/09/2003