

TO: Steve Rhodes, Registration Specialist
Pesticide Registration Branch

FROM: Medical Toxicology Branch

Date: 4/21/03

PRODUCT REGISTRATION RECOMMENDATION SHEET

Formulated Product Name: Etofenprox Technical

Chemical Code #: 2292

ID #: 193825N

EPA Reg. #: 33657-6

SB 950 #: NA

Document #: 51626-002, -005 to -013, and -016 to -020

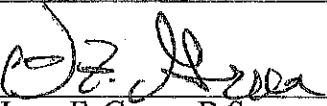
Company Name: Mitsui Chemicals, Inc.

RECOMMENDATION:

Submitted as a Section 3 registration request for manufacturing use only.

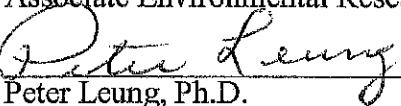
The data reviewed are inadequate for a complete toxicological evaluation. The acute dermal and inhalation toxicity studies are unacceptable but possibly upgradeable with submission of additional data to eliminate the deficiencies indicated in the one-liners. The 90-day inhalation study in rats is unacceptable but may be upgradeable with submission of data and calculations used to determine the reported mean analytical concentrations of the test material. Other unacceptable studies included the chronic oral toxicity study in dogs (inadequate dose level selection) and the rabbit teratology study (incomplete fetal evaluation). The former study may be upgradeable with submission of dose level justification.

Registration is not recommended at this time.

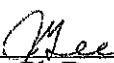

Harry F. Green, B.S.

Associate Environmental Research Scientist

4/23/03
Date


Peter Leung, Ph.D.
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Date


Joyce Gee, Ph.D.
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002; 068280; "Report on Acute Toxicity Study of MTI-500 (Ethofenprox) in Rats" (Hashimoto, K., Hatano Research Institute, FDSC, Kanagawa, Japan, Project No. A-82-27-34, 10/21/82).

002; 068281; "Report on Acute Toxicity Study of MTI-500 (Ethofenprox) in Mice" (Hashimoto, K., Hatano Research Institute, FDSC, Kanagawa, Japan, Project No. A-82-35-42, 10/21/82).

811. MTI-500 (Lot # ST-101, purity = 96%), warmed in a water bath and administered as a singleavage dose to 10 ICR mice per sex per dose at dose levels of 53, 60 and 107.20 g/kg.

811. MTI-500 (Lot # ST-101, purity = 96%), warmed in a water bath and administered as a singleavage dose to 10 ICR mice per sex per dose at dose levels of 53, 60, 110, respectively.

Acute Oral Toxicity

Acute Oral Toxicity LD ₅₀	Acute Dermal Toxicity LD ₅₀	Acute Inhalation Toxicity LC ₅₀	Primary Eye Irritation	Priming Dermatirritation	Dermal Sensitization
IV	IV	Unacceptable but possibly upgradable	IV	IV	Not a sensitizer

Toxicity Category

ACUTE STUDIES - Technical

Submitted for manufacturing use only. Etofenprox is also known as MTT-500.

SUMMARY ("One-liners") from each study worksheet, significant information not mentioned in worksheets, other pertinent information for ongoing review or registration.

Active Ingredient: Biogenprox
Formulated Product Name: Biogenprox Technical
Formulation (excluding inert): 97% Etofenprox, 3% Inerts
Chemical Code #: 193825N
EPA Reg. #: 33657-6
SB 950 #: NA
Document #: 51626-002, -005 to -013, and -016 to -020
Company Name: Mitsui Chemicals, Inc.

DATA PACKAGE SUMMARY AND RECOMMENDATION SHEET - NEW ACTIVE

FROM: Medical Toxicology Branch 4/21/03

Pesticide Registration Branch

Watery diarrhea was observed in all animals beginning 15-20 minutes after dosing with hair around the anus markedly soiled. At 24 hours, soft yellowish stools and anal prolapse were observed in some animals; abdominal swelling, piloerection, facial edema, and soiling of hair over the entire body were also observed. Diarrhea ceased 48 hours after dosing. Necropsy revealed no treatment-related abnormalities. LD_{50} (M/F) > 107.20 g/kg. NOEL not determined. Toxicity Category IV. **Acceptable.** (Corlett, 11/4/02)

Acute Dermal Toxicity

002; 068280; "Report on Acute Toxicity Study of MTI-500 (Ethofenprox) in Rats" (Hashimoto, K., Hatano Research Institute, FDSC, Hatano, Kanagawa, Japan, Project No. A-82-27~34, 10/21/82). 812. MTI-500 (Lot # ST-102, purity = 96%), warmed in a water bath and applied to the clipped skin of 10 Sprague-Dawley rats per sex per dose at a dose level of 2.144 g/kg for 24 hours. No mortalities occurred. Crouching and a reduction in spontaneous movement were observed in all animals 1 or 2 hours after application. Necropsy revealed no treatment-related abnormalities. Reported LD_{50} (M/F) > 2.144 g/kg. Toxicity Category not determined. **Unacceptable but possibly upgradable** with submission of information detailing how the test article was held in contact with the skin during the exposure period. (Corlett, 11/4/02)

002; 068281; "Report on Acute Toxicity Study of MTI-500 (Ethofenprox) in Mice" (Hashimoto, K., Hatano Research Institute, FDSC, Hatano, Kanagawa, Japan, Project No. A-82-35~42, 10/21/82). 812. MTI-500 (Lot # ST-102, purity = 96%), warmed in a water bath and applied to the clipped skin of 10 ICR mice per sex per dose at dose levels of 1.072 and 2.144 g/kg for 24 hours. No mortalities occurred. No clinical signs were observed. Necropsy revealed no treatment-related abnormalities. Reported LD_{50} (M/F) > 2.144 g/kg. Toxicity Category not determined. **Unacceptable but possibly upgradable** with submission of information detailing how the test article was held in contact with the skin during the exposure period. (Corlett, 11/4/02)

Acute Inhalation Toxicity

002; 068282; "MTI-500 Acute Inhalation Toxicity in Rats 4 Hour Exposure" (Jackson, G.C. et al., Huntingdon Research Centre, Huntingdon, Cambridgeshire, England, HRC Report No. MTC 60/821079, 4/2/86 (re-issue)). 813. MTI-500 (Lot No. ST-101, purity = 96%) was blended with acetone, aerosolized, and administered in a whole body manner to 5 COBS® rats per sex at a dose level (reported mean analytical concentration) of 5.9 mg/l (95% of the test material < 5.5 μ m aerodynamic diameter) for 4 hours. No mortalities occurred. Treatment-related clinical signs included closing or partial closing of eyes and dyspnea during exposure, and oily fur, lethargy, hair loss (females only), and hyperactivity during the 14 day observation period. Necropsy revealed no treatment-related abnormalities except for a black area on the liver of 1 male. Reported LC_{50} (M/F) > 5.9 mg/l. Toxicity Category not determined. **Unacceptable but possibly upgradable** with a clarification on the amount of acetone blended with the test material and the submission of the data and calculations used to determine the mean analytical concentration of the test material (Corlett, 10/10/02)

Primary Eye Irritation

002; 068285; "MTI-500 Primary Ophthalmic Stimulation Test in Rabbits" (Kashima, M., Haruna Laboratory, Nippon Experimental Medical Research Institute, Ltd., Agatsuma-gun, Gunma Prefecture, Japan, Project No. Nemri-H-85-55, 10/24/85). 814. 0.1 ml of MTI-500 (Lot No. ST-103, purity = 96.3%) was placed into the conjunctival sac of 1 eye of each of 6 Japanese White rabbits. No corneal opacity or iritis was observed in any treated eye. Grade 1 conjunctival irritation was observed in 5 of 6 treated eyes 24 hours after treatment with all signs of conjunctival irritation clearing in all treated eyes 72 hours after treatment. Toxicity Category IV. **Acceptable.** (Corlett, 10/25/02)

002; 068280; "Report on Acute Toxicity Study of MTI-500 (Ethofenprox) in Rats" (Hashimoto, K., Hatanou Research Institute, FDSC, Hatanou, Kanagawa, Japan, Project No. A-82-27-34, 10/21/82). MTI-500 (Lot # ST-101, purity = 96%), warmed in a water bath and administered subcutaneously into the interscapular region of 10 ICR mice per sex per dose at 10/21/82). MTI-500 (Lot # ST-101, purity = 96%), warmed in a water bath and administered subcutaneously into the interscapular region of 10 ICR mice per sex per dose at 10/21/82). Histopathological examination revealed retention of test material at the test site (in all animals) and swelling of the hair at the test site (in some animals at 53.60 g/kg) were observed.

MTI-500 (Lot # ST-101, purity = 96%), warmed in a water bath and administered subcutaneously to 10 Sprague-Dawley rats per sex per dose at dose levels of 16.08 and 32.16 g/kg and observed for 14 days. No mortalities occurred. Piloerection, transient fluctuations in the frequency of respiration, and crouching were observed in some animals. At 32.16 g/kg, the injection site was markedly swollen after dosing at both 16.08, and 32.16 g/kg. A blood-like substance on the eyelids or nostrils and grayish-white soft stools, swelling of the dorsal neck, and edema over the dorsal neck down to the forelegs were observed in all animals, along with hair soiled by oily dirt and scar formation or depilation at the injection site in some animals. Histopathological examination revealed retention of pale yellow viscous liquid and granuloma formed around the fluid in the subcutaneous tissue of the dorsal neck down to the forelegs with formation of granuloma in the subcutaneous connective tissues and congestion of the liver. LD₅₀ (M/F) > 32.16 g/kg. NOEL not determined.

Supplemental study (not a guideline study) (Corlett, 11/4/02)

account any supplemental information or peer review changes.

SUPPLEMENTAL

002; 068283; "MTI-500 Skin Sensitization Test in Guinea Pigs" (Kobayashi, K., Ozizumi Laboratory, Nippon Experimental Medical Research Institute, Ltd, Ohira-gun, Gunma Prefecture, Japan, no study or project number provided, 10/31/85). 816. A modification of the Magnusson and Kligman maximization assay was used to assess the potential of MTI-500 (lot No. ST-103, and Kligman, no study or project number provided, 10/31/85). 816. A modification of the Magnusson and Kligman maximization assay was used to elicit delayed contact hypersensitivity in the guinea pig. 20 English Hartley guinea pigs were treated with the test material during the induction phase (intradermal injection followed 7 days later by a topical application) and during the challenge phase (topical application followed 7 days later by a topical application). A concurrent negative (topical application of 20 animals was also included in the study. The control animals were treated identically to the test animals except that during induction the test material was replaced with vehicle. Observations 48, and 72 hours after the challenge dose did not indicate any skin-sensitization reaction. Positive controls functional. The results of the study indicate that the test material is not a potential contact sensitizer when using this modified Magnusson and Kligman maximization assay. Accepted. (Corlett, 10/23/02)

Dermal Sensitization

002: 068284; "MTI-500 Primary Skin Stimulation Test in Rabbits" (Kashima, M., Haruna Laboratory, Nippon Experimental Medical Research Institute, Ltd., Agatsuma-guri, Gunma Prefecture, Japan, Project No. Nemri-H-85-5, 8/23/85). 815.5 ml (sic) of MTI-500 (Lot No. ST-103, purity = 96.3%) was applied to the clipped and shaved skin of the back of each of 6 Japanese White rabbits for 4 hours using a semi-occlusive wrap. No edema was observed at any test site. Grade 1 erythema was first observed in 1 animal 48 hours after patch removal, persisting through 7 days after patch removal and clearing 8 days after patch removal. Toxicity Category IV. Acceptable. (Cohleffet, 10/24/02)

Primary Dermal Irritation

site and granuloma formation in the subcutaneous connective tissues at the test site. LD₅₀ (M/F) > 53.60 g/kg. NOEL not determined. **Supplemental study** (not a guideline study) (Corlett, 11/4/02)

002; 068280; "Report on Acute Toxicity Study of MTI-500 (Ethofenprox) in Rats" (Hashimoto, K., Hatano Research Institute, FDSC, Hatano, Kanagawa, Japan, Project No. A-82-27~34, 10/21/82). MTI-500 (Lot # ST-101, purity = 96%), warmed in a water bath and administered intraperitoneally to 10 Sprague-Dawley rats per sex per dose at dose levels of 21.44 and 42.88 g/kg and observed for 14 days. No mortalities occurred. Piloerection and crouching with hollowed belly were observed immediately after dosing at both 21.44 and 42.88 g/kg. Diarrhea or soft stools were observed in all animals the day after test article administration. Necropsy revealed whitish yellow granules adhering to various organs in the abdomen including the fat tissue of the abdominal wall, omentum and mesenterium and around the testes in all animals; hemorrhagic points scattered in the lungs, congestion of the liver, and minor granuloma on the serous membrane of the liver and spleen and on the parietal peritoneum were also observed. LD₅₀ (M/F) > 42.88 g/kg. NOEL not determined. **Supplemental study** (not a guideline study) (Corlett, 11/4/02)

002; 068281; "Report on Acute Toxicity Study of MTI-500 (Ethofenprox) in Mice" (Hashimoto, K., Hatano Research Institute, FDSC, Hatano, Kanagawa, Japan, Project No. A-82-35~42, 10/21/82). MTI-500 (Lot # ST-102, purity = 96%), warmed in a water bath and administered intraperitoneally to 10 ICR mice per sex per dose at dose levels of 6.70, 13.40, 26.80, and 53.60 g/kg and observed for 21 days. Mortalities occurred as follows- males: 2/10, 3/10, 4/10, 3/10, respectively; females: 0/10, 1/10, 7/10, 7/10, respectively. 15 minutes after dosing, reduced appetite and reduced spontaneous movements were observed at all dose levels. 1 day after dosing, piloerection, facial edema, abdominal swelling, and soft stools were observed. Histopathological examination revealed the formation of minor granuloma in the serous membranes of liver, spleen, pancreas, and digestive tract. LD₅₀ (M/F) not determined. NOEL not determined. **Supplemental study** (not a guideline study) (Corlett, 11/4/02)

ACUTE STUDIES - Zoecon F254-87-1 Aerosol

	Toxicity Category
Acute Oral Toxicity LD50	IV
Acute Dermal Toxicity LD50	III
Acute Inhalation Toxicity LC50	IV
Primary Eye Irritation	IV
Primary Dermal Irritation	III
Dermal Sensitization	Not a sensitizer

Acute Oral Toxicity

002; 068288; "Acute Oral Toxicity Study in Rats Administered Test Article Zoecon F254-87-1 Aerosol, Lot No. L255-140-1" (Davis, T.K., UBTL, Inc., Salt Lake City, UT, Study #63296, 5/8/87). 811. Zoecon F254-87-1 Aerosol (Lot No. L255-140-1, 1.3% etofenprox, 0.38% (S)-hydroperene) was administered as a single gavage dose to 5 Sprague Dawley rats per sex per dose at a dose level of 5.1 g/kg. No mortalities occurred. Nasal discharge was observed in 2 animals on the day of dosing clearing in both animals on the next day. Necropsy revealed kidneys exhibiting light red to dark red mottled appearance in 1/5 males and in 2/5 females and each kidney exhibiting 2-12 infarcts in 3/5 males and 3/5 females. LD₅₀ (M/F) > 5.1 g/kg. Toxicity Category IV. **Acceptable.** (Corlett, 10/30/02)

#63300, 5/8/87). 816. A modified version of the Buehler method was used to assess the skin F254-87-1 Aerosol, Lot No. L255-140-1" (Davis, T.K., UBTL, Inc., Salt Lake City, UT, Study 002; 068290; "Dermal Sensitization Study in Albino Guinea Pigs Administered Test Article Zoecoon

Dermal Sensitization

Acceptable. (Corlett, 10/31/02) which all signs of edema clearing in all animals 7 days after patch removal. Toxicity Category III. observed in 3 animals 24 hours after patch removal and in 1 animal 72 hours after patch removal and decreasing to grade 1 in 3 animals 14 days after patch removal. Grade 1 edema was removed, decreasing to grade 2 in 2 animals and grade 1 in 4 animals 7 days after patch removal, rabbits for 4 hours. Grade 2 erythema was observed in all animals 24 and 72 hours after patch removal, (S)-hydroperene) was applied to each of 2 sites on the clipped skin of each of 6 New Zealand 5/8/87). 815. 0.5 ml of Zoecoon F254-87-1 Aerosol (Lot No. L255-140-1, 1.3% etofenprox, 0.38% 87-1 Aerosol, Lot No. L255-140-1" (Davis, T.K., UBTL, Inc., Salt Lake City, UT, Study #63298, 002; 068289; "Primary Dermal Irritation Study in Rabbits Administered Test Article Zoecoon F254-

Primary Dermal Irritation

Toxicity Category IV. Acceptable. (Corlett, 10/31/02) signs of conjunctival irritation clearing in all unashed treated eyes 24 hours after treatment with all conjunctival irritation was observed in 3 of 6 unashed treated eyes 1 hour after treatment with all washed. No corneal opacity or irritation was observed in any unashed treated eye. Grade 1 aerosol (Lot No. L255-140-1, 1.3% etofenprox, 0.38% (S)-hydroperene) was administered to 1 eye of each of 9 New Zealand White rabbits. 3 of the treated eyes were washed and 6 were not aerosol, Lot No. L255-140-1, 1.3% etofenprox, 0.38% (S)-hydroperene) was administered to 1 eye 814. A single 1 second burst from a distance of approximately 10 cm of Zoecoon F254-87-1 Aerosol, Lot No. L255-140-1" (Davis, T.K., UBTL, Inc., Salt Lake City, UT, Study #63299, 5/8/87). 002; 068291; "Primary Eye Irritation Study in Rabbits Administered Test Article Zoecoon F254-87-1

Primary Eye Irritation

(Corlett, 10/29/02) treatment-related abnormalities. $LC_{50} (M/F) > 4.32 \text{ mg/l}$. Toxicity Category IV. Acceptable. and rough and wet fur during exposure; all signs cleared the next day. Necropsy revealed no inactivity, and slightly wet fur during exposure, and red muzzle staining, pale eye color, dandruff, hours. No mortalities occurred. Treatment-related clinical signs included partial closing of eyes, concentration) of 4.32 mg/l (mean mass median particle diameter (GSD) of 3.5 (2.0) μm) for 4 in a whole body manner to 5 CH₃CD₃BR rats per sex at a dose level (mean gravimetric 140-1 and L255-149-1, 1.3% etofenprox, 0.4% (S)-hydroperene) was aerosolized and administered 813. F254-87-1 Aerosol (Lot No. L255- Senneville, Quebec, Canada, Project No. 82969, 6/8/87). 813. F254-87-1 Aerosol (Lot No. L255- 1255-149-1) in the Albino Rat (Safety Test)" (Vau, A. et al., Bio-Research Laboratories Ltd., 002; 068286; "The Acute Toxicity of Inhaled Zoecoon F254-87-1 Aerosol (Lot No. L255-140-1 and

Acute Inhalation Toxicity

III. Acceptable. (Corlett, 10/30/02) and 4 females, no internal abnormalities were observed. $LD_{50} (M/F) > 2.1 \text{ g/kg}$. Toxicity Category and were also observed in some animals. Necropsy revealed dry skin at the exposure site in 1 male were observed. Erythema was observed in all animals after patch removal; edema and eschar dose level of 2.1 g/kg for 24 hours. No mortalities occurred. No treatment-related clinical signs hydroperene) was applied to the clipped skin of 5 New Zealand White rabbits per sex per dose at a 5/8/87). 812. Zoecoon F254-87-1 Aerosol (Lot No. L255-140-1, 1.3% etofenprox, 0.38% (S)- 1 Aerosol, Lot No. L255-140-1" (Davis, T.K., UBTL, Inc., Salt Lake City, UT, Study #63297, 002; 068287; "Acute Dermal Toxicity Study in Rabbits Administered Test Article Zoecoon F254-87-

Acute Dermal Toxicity

sensitization potential of Zoecon F254-87-1 Aerosol (Lot No. L255-140-1, 1.3% etofenprox, 0.38% (S)-hydroprene). 10 Hartley albino guinea pigs were treated with the test material. Induction phase: for each animal, 0.5 ml of the undiluted test article was applied to a pad and placed on a shaved area for 6 hours, 1 application per week for 3 weeks (3 total applications). Each animal was then challenged with the same induction dose at a naive site on each animal, 2 weeks following the third induction dose, for 6 hours. The test material produced a positive result in 20% of the treated animals 48 hours after challenge application. Positive controls functional. **The results of the study indicate that the test material is a potential contact sensitizer when using this modified version of the method of Buehler. Acceptable.** (Corlett, 11/4/02)

SUBCHRONIC STUDIES

(Oral)

007; 186424; "Assessment of the Toxicity of MTI-500 in Rats by Dietary Administration for 13 Weeks" (Green, O.P. et al., Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, England, Laboratory Project ID MTC 56/821067/2, 4/2/86). 821. MTI-500 (Batch No. ST-101, purity = 96%) was admixed to the diet and fed to 20 CD rats per sex per dose at dose levels of 0 (diet and corn oil only), 50, 300, 1800, or 10800 ppm (0, 3.3, 20, 120, 734 mg/kg/day, respectively, for males and 0, 3.8, 23, 142, 820 mg/kg/day, respectively, for females) for 13 weeks. No treatment-related mortalities occurred. No treatment-related clinical signs were observed. A treatment-related decrease in mean thyroxine (T_4) levels in males at 1800 and 10800 ppm was observed. Treatment-related increases in mean adjusted liver weight in males at 10800 ppm and in females at 1800 and 10800 ppm and mean adjusted thyroid weight in males at 1800 and 10800 ppm were observed. Microscopic examination revealed an increased incidence of microfollicles in the thyroid in males at 1800 and 10800 ppm and in females at 10800 ppm and enlargement of the centrilobular hepatocytes in females at 10800 ppm. **No adverse effects.** NOEL (M) = 20 mg/kg/day (300 ppm) based on an increased incidence of microfollicles in the thyroid, NOEL (F) = 23 mg/kg/day (300 ppm) based on increased liver weights and enlargement of the centrilobular hepatocytes. **Acceptable.** (Corlett, 11/22/02)

006; 186423; "Assessment of the Toxicity of MTI-500 to Mice by Dietary Administration for 13 Weeks" (Green, O.P. et al., Huntingdon Research Centre plc, Huntingdon, Cambridgeshire, England, Laboratory Project ID MTC 55/821112/2, 4/2/86). 821. MTI-500 (Batch No. ST-103, purity = 96%) was admixed to the diet and fed to 20 CD-1 mice per sex per dose at dose levels of 0 (diet and corn oil only), 50, 500, 3000, or 15000 ppm (0, 6.1, 60, 375, 1975 mg/kg/day, respectively, for males and 0, 6.9, 71, 390, 2192 mg/kg/day, respectively, for females) for 13 weeks. 2 males and 6 females at 15000 ppm died or were killed for humane reasons and these deaths are considered treatment-related. At 15000 ppm, treatment-related piloerection, hunched posture, emaciated and/or anemic appearance, body tremors, and respiratory distress in both sexes, and lethargy and unsteady gait in females were observed. Treatment-related decreased body weight gain and increased water consumption were observed in both sexes at 15000 ppm. Treatment-related increases in mean urea nitrogen and cholesterol levels and in mean relative liver and kidney weights were observed in both sexes at 15000 ppm. Macroscopic examination revealed kidneys that were pale, enlarged, and with cortical scarring in both sexes at 15000 ppm. Microscopic examination revealed kidneys with widespread tubular basophilia, extensive tubular dilatation, and dilatation of the renal pelvis, centrilobular hepatocyte enlargement, increased cellularity of splenic white pulp, and lymphoid hyperplasia in both sexes at 15000 ppm. **No adverse effects.** NOEL (M) = 375 mg/kg/day (3000 ppm), NOEL (F) = 390 mg/kg/day (3000 ppm) based on kidneys with widespread tubular basophilia and extensive tubular dilatation. **Acceptable.** (Corlett, 11/18/02)

**51626-020 186460, "The Metabolism of ^{14}C -Ethofenprox in Dogs", (D.R. Hawkins, et al., Department of Chemical Metabolism and Radioisotopes, Huntingdon Research Centre, Huntingdon, Cambridgeshire, England, HRC Report No. HRC/MTC 69/84583, 11 October 1985).

Metabolism

METABOLISM STUDIES

Huntingdon Research Centre Ltd, Huntingdon, Cambridgeshire, England, Laboratory Project ID MTC 81/841257, 8/23/85). 824. Ethofenprox (MTL-500, Batch No. ST 103, purity = 96%) was mixed with acetone (90% test article; 10% acetone, w/w), aerosolized, and administered in whole-body manner to 15 Wistar rats per sex per dose at dose levels (reported mean analytical concentration) of 0 (air control), 0 (acetone only), at a concentration equal to the acetone of the test material < 5.5 μ m equivalent aerodynamic diameter) for 6 hours per day 6 days per week for 13 consecutive weeks. No mortalities were reported. Treatment-related scab formation at the back of the ears was observed in males at 1.01 mg/l and in females at 0.21 and 1.01 mg/l. Treatment-related increases in mean liver and thyroid weight in both sexes at 1.01 mg/l and mean adrenal weight in females at 0.21 and 1.01 mg/l were observed. Microscopic examination revealed increased enlargement of adrenals in males at 1.01 mg/l, and a minimally increased cortical width of adrenals in females at 0.21 and 1.01 mg/l. No adverse effects. NOEL (M) = 0.21 mg/l based on increased liver and thyroid in males at 1.01 mg/l, and a minimally increased cortical width of adrenals in females at 0.21 and 1.01 mg/l. No adverse effects. NOEL (F) = 0.042 mg/l based on enlarged adrenals and increased adrenal weight in the thyroid; NOEL (F) = 0.042 mg/l based on increased corticosteroids and increased adrenal weight together with the submission of the data and calculations used to determine the reported analytical concentrations of the test material. (Cottert, 12/3/02)

008; 186425; "A 28-Day Repeated Dose Dermal Toxicity Study in Rabbits with Technical M11-500" (Kileen, J.C., Jr., Toxicology & Metabolism, Ricercra, LLC, Palmerville, OH, Document No. 011077-1, 6/28/00). 870.32, Technical M11-500 (Lot No. 21049, purity = 99.18%) was applied to the clipped dorsal skin of 10 New Zealand White rabbits per sex per dose at doses of 0 (tap water only), 400, 650, or 1000 mg/kg/day for 6 hours per day, for 28 consecutive days. In addition, 10 animals per sex at the control and high dose levels were used to assess recovery (recovery group animals were observed for an additional 2 weeks after the others were sacrificed). No mortalities occurred. No treatment-related systemic clinical signs were observed. Body weight and organ weight determinations along with hematology and serum chemistry revealed no treatment-related effects. Treatment-related erythema at the test site was observed at the 400, 650 and 1000 mg/kg/day dose levels in both sexes throughout the 28-day treatment period. Microscopic examination revealed treated skin where the epidermis exhibited treatment-related diffuse hyperplasia at 400, 650, and 1000 mg/kg/day in both sexes; treated recovery group animals did not significantly exhibit this effect. NO adverse effects. NOEL (M/F, systemic) = 1000 mg/kg/day based on no treatment-related effects at the highest dose tested; NOEL (M/F, skin) < 400 mg/kg/day based on incidences of erythema and epidermis with diffuse hyperplasia. (Inhalation) (Corlett, 12/11/02)

(Dermal)

dosing. Excretion of radioactivity in urine (including cage wash) accounted for a mean of 6.2% of dose in 5 days of which 5.0% was eliminated within 24 hours after treatment. Unchanged ethofenprox accounted for 91.4% and 93.3% of the radioactivity extracted from feces (0-24 hours post-dosing) of males and females respectively, equivalent to 48.5% and 59% of the dose respectively. The next most plentiful components in feces were 2 metabolites, one from O-deethylation of the ethoxyphenyl moiety, and, the other, from aromatic ring-hydroxylation of the phenoxybenzyl moiety of ethofenprox. They accounted for 6.1% (male) and 4.6% (female) of extracted radioactivity, equivalent to 3.5% and 2.9% of the administered dose respectively. Plasma concentrations peaked from 15 minutes to 3 hours after dosing at 4.43 to 7.16 µg/ml. Plasma concentration half-lives were between 8.6 and 17 hours. The highest tissue concentrations of radioactivity were found in the liver (range 3.1 to 9.6 µg/g). Whole liver contained between 0.25% and 0.91% dose in the four animals. Next highest concentrations were found in kidneys and fat. Lowest concentrations were in muscle. Bile, from the gall bladders of 2 animals, contained very high radioactivity levels. **Acceptable.** (Green and Gee, 4/10/03).

**51626-020 186461, "The Biokinetics and Metabolism of ¹⁴C-Ethofenprox in the Rat", (D. R. Hawkins, et al., Department of Chemical Metabolism and Radiosynthesis, Huntingdon Research Centre, Huntingdon, Cambridgeshire, England, HRC Report No. MTC 68/84610, 1 August 1985). Single (30 and 180 mg/kg) and multiple (30 mg/kg/day for 7 or 14 consecutive days) doses of ¹⁴C-ethofenprox were used for groups of 3, 5, or 25 CD rats per sex or 3 or 10 pregnant/lactating females per group to evaluate metabolic and pharmacokinetic parameters.

A single oral dose of ¹⁴C-ethofenprox at 30 mg/kg to 5 rats per sex was mainly eliminated in the feces. During the 5 days following dosing, means of 88.0% and 86.4% dose were excreted by males and females respectively by this route. Approximately equal amounts (35% to 40% of dose) were excreted by both sexes during the 0 to 24 hour and 24 to 48 hour periods. Excretion of radioactivity in the urine accounted for means of 10.8% (males) and 8.0% (females) over 5 days and most was excreted in the first 24 hours. Mean total retention of radioactivity in the bodies 5 days post-dosing was 3.4% (males) and 3.5% (females). The pattern of excretion of radioactivity after a single oral dose of ¹⁴C-ethofenprox to 5 per sex at 180 mg/kg was similar to that seen at 30 mg/kg. Tissue concentrations of radioactivity were measured at 120 hours after dosing. Highest mean tissue concentrations were found in fat of 30 mg/kg dosed animals (16.6 µg/g in males, 11.1 µg/g in females). Muscle concentrations were near the limit of accurate measurement (0.05 µg/g). Liver contained mean concentrations of 0.34 µg/g (males) and 0.33 µg/g (females). Mean kidney concentrations were 0.13 and 0.16 µg/g for males and females respectively. At 180 mg/kg, mean fat concentrations of radioactivity were 90.2 µg/g and 94.0 µg/g for males and females respectively 120 hours after dosing. Concentrations in other tissues were all below 2 µg/g. Unchanged ethofenprox accounted for 6.6% and 14.0% of dose for males and females respectively at 30 mg/kg, and, for 22.6% and 29.0% respectively at 180 mg/kg in extracts of rat feces collected during 72 hours. The metabolite desethylethofenprox was 19.5% (males) and 25.1% (females) at 30 mg/kg and 23.2% and 20.6% respectively at 180 mg/kg over the same time period. Another metabolite, 4'-hydroxyethofenprox, made up 13.2% and 13.8% at 30 mg/kg and 7.2% and 8.1% at 180 mg/kg of the extracts for males and females respectively.

After a single oral dose at 30 mg/kg to 5 per sex, peak plasma concentrations (approximately 5 µg/ml) occurred 2 to 7 hours later. Peak plasma concentrations (16 µg/ml to 17 µg/ml) were reached 5 hours post-dosing after a single dose of 180 mg/kg.

In a tissue distribution assay, 30 mg/kg/day of ¹⁴C-ethofenprox was administered to 25 rats per sex on seven consecutive days. 5 per sex were sacrificed for sampling at 4, 24, 48, 120, and 240 hours after the last dose. The highest concentrations of radioactivity in all tissues were found at 4 hours post-dosing. Fat contained the highest concentration (94.2 µg/g to 101 µg/g). Next highest concentrations (30.5 µg/g male, 22.3 µg/g female) were found in liver at 4 hours. The major component in fat and liver was unchanged ethofenprox.

10 pregnant female rats received 30 mg/kg/day of ¹⁴C-ethofenprox by oral intubation on gestation days 10 through 16. 2 dams were sacrificed for sampling at 4, 24, 48, 72, and 120 hours after

***51626-011, 012 186428, 186439, "Ethofenprox (MTI 500) Potentiation of Tumorigenic and Toxic Effects in Prolonged Dietary Administration to Rats (Final Report)", (Owen P. Green, et al., Huntington Research Centre Ltd, Huntington, Cambridgeshire, England, Report # MTC 59/85581, 24 January 1986). 70 CD rats per sex per group of Sprague-Dawley origin received 44900 ppm for 110 weeks. 50 and 20 animals per sex per group were designated main and satellite groups respectively. Main group animals were used for tumorigenic evaluation through 110 weeks of treatment. Satellite animals were used for blood and urine sampling at intervals and for interim sacrifice after 26 and 52 weeks of treatment. Group mean mg/kg/day 34% reductions in body weight gain were recorded for males and females receiving 44900 ppm throughout the treatment period. Marginally lower water intakes were noted for males and females receiving 4900 ppm during weeks 5, 12, and 23. Statistically significant increases in absolute liver weight were recorded in both sexes at 4900 ppm for weeks 26, 52, and 110. Relative (% of bodyweight) liver weights were also increased. Absolute and relative thyroid weights were higher for 4900 ppm males at weeks 26 and 106 and for 700 ppm males at termination. Absolute (with statistical significance) and relative kidney weights were increased for

SB950-MANDATED HEALTH EFFECTS STUDIES

Secretion of radiactivity into the milk of mother rats was evaluated by analysis of the stomach contents of suckling pups. Dams were treated with 30 mg/kg/day of ¹⁴C-ethofenprox by oral intubation from gestation day 18 through lactation day 9 (14 days total). Radiactivity concentrations ranged from 41.3 $\mu\text{g/g}$ to 88.3 $\mu\text{g/g}$ after one hour of suckling compared to maternal plasma concentrations in the range of 1.9 $\mu\text{g/ml}$ to 3.6 $\mu\text{g/ml}$. Chromatographic analysis indicated that 95% of the radiactivity ingested by the pups was associated with unchanged ethofenprox. Acceptable. (Green and Gee, 4/10/03).

**51626-020 186462, "Dermal Absorption of ¹⁴C-Etofenprox in Male Rats (Preliminary and Definitive Phases)", Fred Thalacker, Covance Laboratories, Inc., Madison, WI, Laboratory Project Number CHW 6648-135, 4 January 1999. Shaved, washed, unbarred skin of the back and shoulders (12.5 cm²) of 16 CD BR SD male rats per group was treated (non-occlusive) once with ¹⁴C-Etofenprox (MTL-500) at 5, 59, and 184 $\mu\text{g/cm}^2$. 4 animals per group were sacrificed for analysis at 1, 10, 24, and 96 hours post-dosing. The skin at the application site was washed using 2 % Ivory soap just before sacrifice (1-and 10-hour sacrifice animals) or 10 hours after treatment (24- and 96-hour sacrifice animals) and the wash retained. Overall recoveries of radiactivity, including all time points, were 94.9%, 97.9%, and 122% of the total dose at 5, 59, and 184 $\mu\text{g/cm}^2$ respectively. Most of the radiactivity detected in or on skin was 4.59% to 13.5% (low dose), 7.07% to 18.1% (mid dose), and 8.52% to 30.3% (high dose). The percentage of applied radioactivity absorbed (found in blood, carcass, and excreta (urine, feces, cage wash and cage wipe)) was 5.07%, 6.10%, and 6.57% at 5, 59, and 184 $\mu\text{g/cm}^2$ after 96 hours. Acceptable. (Green and Gee, 3/13/03).

The last dose. Adrenal glands, kidneys, heart, and liver showed radioactivity concentrations and patterns of elimination of radioactive similar to non-pregnant animals. Of those, adrenal glands contained the highest concentrations, 61.5 \mu g/g at 4 hours, declining to 5.74 \mu g/g at 120 hours. Of the reproductive tissues, mammary contained the highest concentrations (87.4 \mu g/g at 4 hours declining to 32.4 \mu g/g at 120 hours after the last dose), similar to those in fat of non-pregnant animals. Radioactivity concentrations in placenta were lower than in any other maternal tissue. Concentrations declined from 4.6 \mu g/g to 4.8 \mu g/g at 4 hours to 0.17 \mu g/g at 120 hours. Maximum fetal concentrations were 1.6 \mu g/g to 1.7 \mu g/g at 4 hours.

4900 ppm females at week 26 and for 700 and 4900 ppm males at week 52. Increased liver enlargement for 4900 ppm males at scheduled and unscheduled sacrifice, and for females at 26 week sacrifice was noted. At termination, pale focus/foci in the lungs was increased in males and females at 4900 ppm. Enlarged thyroid was increased in 4900 ppm females at terminal sacrifice. Thyroid adenomas plus carcinomas were increased at 4900 ppm with a positive significant trend in males and a significant increase in females by pair wise comparison (0/50 versus 9/50). Non-neoplastic changes were observed as increased centrilobular hepatocyte enlargement at 26 week sacrifice (satellite) and at termination (main) in 4900 ppm animals and as increases in eosinophilic hepatocytes in main group animals at 700 and 4900 ppm. **Chronic NOEL** = 100 ppm (non-neoplastic liver changes, reduced bodyweight gain and food consumption). **Possible adverse effects** (thyroid tumors at 4900 ppm). 186439 is a photomicrography addendum for histopathology. **Acceptable.** (Green and Gee, 4/3/03).

Chronic Toxicity, Dog

51626-010 186427, "Ethofenprox (MTI-500) Toxicity to Dogs by Repeated Dietary Administration for 52 Weeks Followed by a Recovery Period of 8 Weeks", (Robert J. Harling, *et al.*, Huntingdon Research Centre, Ltd., Huntingdon, Cambridgeshire, England, Report # MTC 71/85234, 25 October 1985). 6 (control and high dose) or 4 Beagle dogs per sex per group received ethofenprox (MTI-500) (96.3% purity) in the diet at 0 (basal diet + corn oil), 100, 1000, and 10000 ppm for 52 weeks. In a recovery phase, 2 animals per sex from the control and high dose groups received untreated diet for 8 weeks following treatment. Mg/kg/day equivalents for males and females were 3.46 and 3.17; 33.37 and 32.19; and 351.73 and 339.32 at 100, 1000, and 10000 ppm respectively. Statistically significant decreases in total protein and cholesterol and increases in alkaline phosphatase were noted for 10000 ppm males and females from week 6 onwards. NOEL = Cannot be determined. After 52 weeks of treatment, lung, liver, kidney, and pancreas weights (as % of bodyweight) were increased (statistical significance for liver) for both sexes at 10000 ppm relative to controls. One 1000 ppm female and 2 males and 1 female at 10000 ppm were noted with accentuation of the lobular markings of the liver at 52 week necropsy. Histopathology revealed 2/4 female dogs at 10000 ppm with minimal swelling of centrilobular liver cells at 52 weeks. The noted changes were generally diminished or absent after the 8 week recovery period. **No adverse effects. Unacceptable**, upgradeable (with dose level justification). (Green and Gee, 4/10/03).

Oncogenicity, Mouse

**51626-013, 016 186440, 186443, "Ethofenprox (MTI-500) Potential Tumorigenic and Toxic Effects in Prolonged Dietary Administration to Mice (Final Report)", (Owen P. Green, *et al.*, Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, England, Report # MTC 58/85582, 6 January 1986). Seventy-six CD-1 mice (of Swiss origin) per sex per group received ethofenprox (MTI-500) technical (96.3%) in the diet at 0 (basal diet + corn oil), 30, 100, 700, and 4900 ppm for 108 weeks. Fifty-two per sex per group, designated main group animals, were treated through 108 weeks. The remaining 24 per sex per group satellite animals were used for blood and urine sampling at intervals through week 52 and for interim necropsies at 26 and 52 weeks. Mean mg/kg/day intake of ethofenprox for weeks 1 through 108 was 3.1 and 3.6, 10.4 and 11.7, 75.2 and 80.9, and 546.9 and 615.5 mg/kg/day for males and females at 30, 100, 700, and 4900 ppm respectively. For males at 4900 ppm, survival was reduced at study termination and bodyweight gain was decreased through week 52. Water consumption increased (statistically significant) for both sexes at 4900 ppm for weeks 5, 12, and 23 and urine volume was higher (statistically significant) for males at all treatment levels at week 52. Absolute (g) liver weights were higher (statistically significant) for males at 4900 ppm and relative liver weights (% bodyweight) were increased for both sexes. Also at necropsy, in both sexes, the incidence of pale kidneys was increased at 100, 700, and 4900 ppm and renal cortical scarring incidence was higher at 4900 ppm. Treatment related non-neoplastic changes were confined to the kidney. Increases in dilated/basophilic cortical tubules of varying severity were noted for both sexes at 100, 700, and 4900 ppm and for males at 30 ppm. This lesion was associated with focal loss of

Teratology, Rat

Acceptable. (Green and Gee, 4/9/03).

= 700 ppm (lower pup weight and pup loss (days 12 to 21) at 4900 ppm). No adverse effects.

700 ppm (cytic collecting in kidneys (days at 4900 ppm). Reproductive NOEL = 4900 ppm. Pup NOEL = 700 ppm (reproductive organs/tissues, a thorough exam was done on the F1b adults. Parental NOEL = 700 ppm (cytic collecting in kidneys (days at 4900 ppm). Reproductive NOEL = 4900 ppm. Pup NOEL = 700 ppm (follicular epithelium in males (6/23) at 4900 ppm. Although histopathology was not conducted on both sexes at 4900 ppm. Thyroid changes were limited to minimal increased height of the seen in FO kidneys. In the liver, minimal centrilobular hepatocytic enlargement was recorded in One 700 ppm female was also noted with cystic collecting ducts. Some of these effects were not incidence of dilated coxial tubules in males. Coxial scarring and an increased necrosis or pyelonephritis was observed in some animals. Coxial scarring and an increased vasculär congestion or hemorrhage in the medulla. Foreshortening of the papilla, papillary ducts were noted and were often associated with focal medullary fibrosis, mineral deposits, and Histopathology indicated changes in the kidneys of F1b animals at 4900 ppm. Cystic collecting enlarged/swollen/misshapen kidneys for F1a, F1b, and F2b adults and weanlings at 4900 ppm. thyroid weights were increased at 4900 ppm in both sexes. Necropsy showed an increase in 14. FO and F1b female bodyweights at 4900 ppm were lower (5% to 7%) than controls generally during weeks 4-14 of treatment. Relative (% of bodyweight) F0, F1, and F2b liver, kidney, and F2b adults at 4900 ppm relative to controls for various time periods during weeks 5 through twice. F2 (F2b) animals were reared to maturity. Water consumption was increased for F1a, F1b, maturing through 2 matings. Twenty-four F1 (F1b) animals per sex per group were allowed to mate 0 (SF) Laboratory Animal Diet No. 2 + corn oil), 100, 700, and 4900 ppm starting 70 days pre- CD(SD)BR rats per sex per group received Ethofenprox (MTI-500) technical (96.3%) in the diet at England, Report No. MTC 67/85706, 9 October 1985). In the FO generation, 28 CH:COBS (David D. Cozens, et al., Huntingdon Research Centre, Ltd., Huntingdon, Cambridgeshire,

**51626-018 186473, "Effect of Ethofenprox (MTI-500) on Multiple Generations of the Rat",

Reproduction, Rat

for thyroid tumor induction and the use of a MOE. (Green and Gee, 4/03/03).

186442 were not given a review. The argument was being made for a non-genotoxic mechanism containing full copies of published literature listed in the references of 186441. Publications in indicated more variability for thyroid effects than in the initial evaluation. Record 186442 appended broadening of the historical control pool that included more data for the strain from the rat supplier the in vitro based effect of ethofenprox on FR TL 5 (Fischer rat thyroid follicular cells). The oncogenicity. Also, on results of the in vitro studies (non-guideline protocols) in the appendix on the negative results of mice and dog studies previously conducted showing no thyroid Oncoxygen on the basis of increased incidence (outside the historical control range for the Oncoxygen on the basis of increased incidence (outside the historical control range for the performing laboratory) of thyroid follicular cell adenomas and carcinomas combined in the rat. The authors requested a reclassification for ethofenprox to Group D or E Oncoxygen based on the negative results of mice and dog studies previously conducted showing no thyroid oncoxygenicity. Acceptable. (Green and Gee, 4/2/03).

tubules at the higher dose levels. No carcinogenicity, no adverse effects. Chronic NOEL = 30 ppm (3.1 and 3.6 mg/kg/day in males and females respectively) (kidney changes). Record 186443 contains a photomicrography addendum for kidney changes. No evidence of oncoxygenicity. Acceptable. (Green and Gee, 4/2/03).

ethofenprox. The untreated reproductive phase continued through weaning of the F2 generation.

Teratogenicity phase results: Increased salivation was noted for dams at 250 and 5000 mg/kg/day. Wet/brown staining around the mouth and wet/yellow stained fur around the anogenital region were increased at 5000 mg/kg/day. The incidence of fetal visceral malformations was slightly higher at 5000 mg/kg/day. One fetus from each of 3 females was effected. 1 fetus with left microphthalmia, another with internal hydrocephaly and absent innominate artery, and a third with right microphthalmia and left anophthalmia were noted. The incidence was not statistically significant on a litter basis. **Maternal NOEL = 250 mg/kg/day** (increased wet/brown staining around the mouth and wet/yellow stained fur around the anogenital region at 5000 mg/kg/day). **Developmental NOEL = 5000 mg/kg/day.** **Reproductive assessment phase:** Time to vaginal opening was marginally earlier for F1 females (exposed *in utero*) relative to controls. In the hole-board test, F1 males and females in the 250 and 5000 mg/kg/day groups showed slightly lower mobility than controls. Rearing counts were also lower for males in these groups. F1 females from all treatment groups also had slightly longer entry times on day 1 and 2 in the passive avoidance test. F2 generation litter results were generally in line with controls. **Acceptable** with no teratogenicity. (Green, Gee, and Leung 4/4/03).

Teratology, Rabbit

51626-017 186451, "Rabbit Developmental Toxicity Study with Etofenprox", (James L. Ivett, Covance Laboratories, Inc., Vienna, VA., Covance study No. 6648-144, 17 January 2001). 20 mated Hra:(NZW)SPF female rabbits per group were dosed by oral gavage with Etofenprox technical (96.68% purity) at 0 (1% aqueous methylcellulose), 30, 100, and 300 mg/kg/day on gestation days 6 through 28. There were no signs of maternal toxicity in any of the dose groups including clinical signs, bodyweights, bodyweight change, and food consumption. No external findings in any of the fetuses were recorded. No changes in fetal viability or fetal weight were indicated. **Maternal NOEL = 300 mg/kg/day.** Developmental NOEL was not determined due to incomplete fetal evaluation. **Unacceptable, not upgradeable** (incomplete fetal visceral exam, no skeletal exam). (Green and Gee, 4/4/03).

51626-017 186450, "Dose Range-Finding Developmental Toxicity Study in Rabbits with Etofenprox", (James L. Ivett, Covance Laboratories, Inc., Vienna, VA, Covance Study No. 6648-143, 13 September 2000). Five mated Hra:(NZW)SPF female rabbits per group received etofenprox (96.68% purity) by oral gavage at 0 (1% methylcellulose), 50, 125, 250, and 500 mg/kg/day on gestation days 6 through 28. At 500 mg/kg/day, the incidence of dams with thin appearance and few or no feces was increased. Maternal bodyweight and food consumption were reduced and the number of abortions increased (3/5). Fetal viability and weight were also reduced at 500 mg/kg/day. **Maternal and Developmental NOEL = 250 mg/kg/day.** **Supplemental information.** (Green and Gee, 4/4/03).

Gene Mutation

51626-019 186454, "Reverse Mutation in *Salmonella typhimurium*", (C.N. Edwards and R. Forster, Life Science Research, Roma Toxicology Centre, Rome, Italy; LSR-RTC Report No. 162001-M-06185, 22 August 1985). *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 were exposed (triplicate plates, 2 trials) to ethofenprox (MTI-500) (96.3% purity), in the presence and absence of S9 activation, at 0 (DMSO), 200, 400, 800, 1600, and 3200 µg/plate for 72 hours. A precipitate formed at 3200 µg/plate. Positive controls were functional. No increase in revertant colonies. **Acceptable. (Green and Gee, 3/10/03).

**51626-019 186452, "Gene Mutation in Chinese Hamster V79 Cells", (A. H. Seeberg and R. Forster, Life Science Research, Roma Toxicology Centre, Rome, Italy, LSR-RTC Report No. 162002-M-06985, 22 August 1985). Chinese hamster V79 cells were exposed in triplicate (2 trials) to Ethofenprox (MTI-500) (96.3% purity) in the presence and absence of rat liver S9 activation at 0 (1% dimethylsulfoxide), 9.75, 19.5, 39.0, 78.0, and 156.0 µg/ml (limit of solubility)

**51626-019 186457, "In Vitro Assessment of the Cytotoxicity of MTI-500 a-CO in Cultured Human Peripheral Lymphocytes", (J. Bootman et al., Life Sciences Research Limited, Eye, Suffolk, England, LSR Report No. 85/MTO021/711, 22 November 1985). Cultures of male human blood lymphocytes in whole blood exposed to MTI-500 a-CO (99.6%) in triplicate at 0 (DMSO), 0 (untreated medium), 2.5, 5.0, 10.0, and 20.0 μ g/ml in the absence of S9 activation and (DMSO), 0 (untreated medium), 37.5, 75.0, and 300 μ g/ml in the presence of S9 activation and S9. Cultures were treated for 24 hours (activated cultures were washed after 2 hours, then re-treated (without activation) for a further 22 hours). One hundred metaphases were scored per culture. Mitotic indices were used for evidence of toxicity. No increase in structural chromosomal aberrations. Positive controls were functional. Acceptable. (Green and Gee, 3/10/03).

**51626-019 186458, "MTI-500 a-CO: Assessment of its Ability to Cause Lethal DNA Damage in Strains of Escherichia Coli", (J. Bootman and K. May, Life Sciences Research Limited, Eye, Suffolk, England, LSR Report No. 85/MTO022/504, 2 October 1985). Duplicate suspensions (2-5 x 10⁶ cells/ml) of Escherichia coli strains WP2, WP67, and CM871 were exposed in the presence and absence of rat liver S9 activation to MTI-500 a-CO (99.6%) at 0 (DMSO), 0 (untreated), 320, 1000, 3200, and 10000 μ g/ml for 2 and 18 hours. Bacteria were diluted and plated in duplicate colonies per plate scored after 1 day at 37°C. Cell lethality was not increased in repair deficient strains (WP67 and CM871). Positive controls (2-aminoanthracene and mitomycin) were number of colonies per strain (WP67 and CM871). Cell lethality was not increased in repair deficient strains (WP67 and CM871). Positive controls (2-aminoanthracene and mitomycin) were number of colonies per strain (WP67 and CM871). Cell lethality was not increased in repair

DNA Damage

51626-019 186455, "MTI-500, Ethofenprox: Assessment of Clastogenic Action on Bone Marrow Erythrocytes in the Micronucleus Test", (J. Bootman, et al., Life Science Research, Eye, Suffolk, England, LSR Report No. 85/MTO016/406, 3 July 1985). 15 (control and high dose) or 5 CD-1 mice per sex per group received a single oral gavage dose of ethofenprox (MTI-500) at 0 (0.5% methylcellulose), 80, 400, and 2000 mg/kg. 5 mice per sex per group were sacrificed 24 hours after treatment for bone marrow evaluation. Further lots of 5 animals per sex from the control and high dose groups were sacrificed 48 and 72 hours post-dosing. Approximately 2000 erythrocytes were scored per animal. The positive control, chlorambucil, was functional. No increase in micronucleated polychromatic erythrocytes. **Acceptable. (Green and Gee, 3/10/03).

51626-019 186456, "In Vitro Assesment of the Clastogenic Activity of MTI-500, Ethofenprox, in Cultured Human Peripheral Lymphocytes", (J. Bootman, et al., Life Science Research Limited, Eye, Suffolk, England, LSR Report No. 85/MTO017/430, 17 July 1985). Triplicate cultures of male human blood lymphocytes were exposed to ethofenprox (MTI-500) (96.3%) at 0 (DMSO), 6.25, 12.5, 25.0, and 50.0 μ g/ml in the presence and absence of rat liver S9 activation for 2 and 24 hours respectively (activation for 22 hours). Triplicate cultures with 100 metaphases activated further (activation for 2 hours), then re-treated (without activation) for a further 22 hours. Positive controls were re-coded. Positive controls were functional. No increase in structural chromosomal aberrations. **Acceptable. (Green and Gee, 3/10/03).

Chromosome Effects

**51626-019 186453, "MTI-500 a-CO: Assessment of its Mutagenic Potential in Amino-Acid Auxotrophs of *Salmonella typhimurium* and *Escherichia coli*" (J. Bootman and K. May, Life Sciences Research Limited, Eye, Suffolk, England, LSR Report No. 85/MT0020/433, 19 July 1985). *Salmonella typhimurium* strains TA 97a, TA 98, TA 100, TA 102, TA 1535, and TA1537 and *Escherichia coli* strain WP2 uvrA were exposed, in triplicate, in the presence and absence of rat liver S9 activation, to MTI-500a-CO (99.6% purity) at 0 (DMSO), 50, 158, 500, 1582, and 5000 µg/plate, for 48 hours. No increase in mutation frequency. Positive controls were functional.

for three hours. No increase in mutation frequency for 6-thioguanine resistance. **Acceptable.** (Green and Gee, 3/10/03).

51626-019 186459, "Unscheduled DNA Synthesis in Human Cells, Cell Line: Hela S3" (A.H. Seeberg and R. Forster, Life Science Research, Rome, Italy, LSR-RTC Report No. 162003-M-05785, 30 July 1985). Human Hela S3 cells were exposed to ethofenprox (MTI-500) (96.3%) in triplicate monolayer cultures at 0 (DMSO), 2.44, 4.88, 9.75, 19.5, and 39.0 µg/ml in the presence of rat liver S9 mix and at 0 (DMSO), 9.75, 19.5, 39.0, 78.0, and 156 µg/ml without S9 for 3 hours in the presence of [³H] thymidine in two trials. The highest concentration was based on toxicity and solubility. Replicative DNA synthesis was suppressed in arginine free medium and by hydroxyurea during exposure. DNA was extracted from cell pellets by trichloroacetic acid precipitation followed by hydrolysis in 0.3 M KOH with heating. Label incorporation was determined by LSC and DNA concentration by a colorimetric assay. Results were expressed as DPM/µg DNA. Positive controls (4-NQO and B(a)P) were functional. No increase in unscheduled DNA synthesis. **Acceptable. (Green and Gee, 4/9/03).

STUDIES ON METABOLITES

005; 186415; "MTI-500 α-Co: Acute Toxicity Study in the Rat" (Cummins, H.A. and Gardner, J.R., Life Science Research Limited, Eye, Suffolk, England, Laboratory Project ID 85/MT0018/474, 8/2/85). MTI-500 α-Co (Batch OFU-1021, purity = 99.6%), suspended in maize oil, was administered as a single gavage dose to 5 CD rats (remote Sprague-Dawley origin) per sex at a dose level of 5000 mg/kg. No mortalities occurred. Decreased motor activity was observed in all animals 2 hours after dosing clearing in all animals 4 hours after dosing. Necropsy revealed dark submandibular salivary glands in 2 males and large cervical lymph nodes in 1 male. LD₅₀ (M/F) > 5000 mg/kg. NOEL not determined. **Supplemental study** (the test material used in the study was not the active ingredient in review) (Corlett, 11/6/02)

005; 186416; "Ethofenprox (MTI-500) Acute Limit Test of Toxicity to Dogs Following a Single Oral Administration" (Harling, R.J. et al., Department of Dog Toxicology, Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, England, Laboratory Project ID MTC 101/851185, 10/24/85). Ethofenprox (MTI-500) (Batch ST103, purity = 96.3%) was inserted into gelatine capsules and 1 pure-bred beagle dog per sex was dosed once with 5000 mg/kg. No mortalities occurred. Semi-soft green feces approximately 2 hours after dosing and semi-soft feces of normal color on Days 2 and 4 were observed in the male; no clinical signs were observed in the female. Small weight loss was observed in the female for 3 days following dosing and at the end of the 14 day observation period. Necropsy revealed no treatment-related abnormalities. Bone marrow smears taken from each animal prior to terminal sacrifice were found to be normal in cellularity, morphology, and cell distribution. LD₅₀ (M/F) > 5000 mg/kg. NOEL not determined. **Supplemental study** (only 1 animal per sex per dose group used) (Corlett, 11/6/02)

CONCLUSIONS: Do data support registration?

Toxicity data were submitted to support a Section 3 registration request for Etofenprox Technical for manufacturing use only.

The acute oral toxicity and primary dermal and ocular irritation studies are acceptable. In contrast, the acute dermal and inhalation toxicity studies are unacceptable but possibly upgradeable with submission of additional data to eliminate the deficiencies indicated in the one-liners above. MTI-500 is not a potential dermal sensitizer as indicated by the dermal sensitization study. Acceptable acute studies were submitted for a formulated product, Zoecon F254-87-1 Aerosol.

Subchronic oral feeding studies with rodents and 28-day repeated dose dermal toxicity studies are acceptable. However, the 90-day inhalation study in rats is unacceptable but may be upgradeable

The data reviewed are inadequate for a complete toxicological evaluation. The acute dermal and inhalation toxicity studies are unacceptable but possibly upgradeable with submission of additional data to eliminate the deficiencies indicated in the one-liners. The 90-day inhalation study in rats is unacceptable but may be upgradeable with submittion of additional mean analytical concentrations of data to determine the test material. Other unacceptable studies included the chronic oral toxicity study in dogs (inadequate dose level selection) and the rabbit teratology study (incomplete fetal evaluation). The former study may be upgradeable with submission of dose level justification.

Submitted as a Section 3 registration request for manufacturing use only.

RECOMMENDATIONS: What type of registration action is being considered? In the case of analogous registration, register or do not register? What other specific studies or data are requested?

Acceptable studies were submitted to satisfy the current data requirements for gene mutation, chromosomal effects and DNA effects.

The rat developmental and reproduction studies are acceptable. The rabbit teratology study is not acceptable due to incomplete fetal evaluation.

Chromic feeding studies in rodents (rats and mice) are acceptable. However, the chronic toxicity study in dogs is not acceptable but may be upgradeable with submission of additional data to justify the dose levels selected.

Animal metabolism studies in dogs and rats were submitted. Collectively, the data fulfills the current requirements for an acceptable metabolism study.

With submission of data and calculations used to determine the reported mean analytical concentrations of the test material.

TO: Steve Rhodes, Senior Pesticide Use Specialist
Pesticide Registration Branch

FROM: Medical Toxicology Branch

Original Date: 4/21/03
Revised: 7/28/03

PRODUCT REGISTRATION RECOMMENDATION SHEET

Formulated Product Name: Etofenprox Technical
Chemical Code #: 2292 **ID #:** 193825N
EPA Reg. #: 33657-6 **SB 950 #:** NA
Document #: 51626- 002, -005 to - 013, and -016 to -020, -023
Company Name: Mitsui Chemicals, Inc.

RECOMMENDATION:

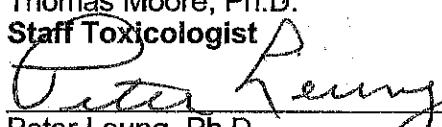
Submitted as a Section 3 registration request for manufacturing use only.

The data reviewed are inadequate for a complete toxicological evaluation. The acute inhalation toxicity study is unacceptable but possibly upgradeable with submission of additional data to eliminate the deficiencies indicated in the one-liners. The 90-day inhalation study in rats is unacceptable but may be upgradeable with submission of data and calculations used to determine the reported mean analytical concentrations of the test material. Another unacceptable study is the chronic oral toxicity study in dogs (inadequate dose level selection). This study may be upgradeable with submission of dose level justification.

Registration is not recommended at this time.


Thomas Moore, Ph.D.

Staff Toxicologist


Peter Leung, Ph.D.

Senior Toxicologist


Joyce Gee, Ph.D.

Senior Toxicologist


Date


Date


Date

002; 068281; "Report on Acute Toxicity Study of MTI-500 (Etofenprox) in Mice" (Hashimoto, K., Hatano Research Institute, FDSC, Hatano, Kanagawa, Japan, Project No. A-82-35~42, 10/21/82). 811. MTI-500 (Lot # ST-101, purity = 96%), warmed in a water bath and administered as a singleavage dose to 10 ICR mice per sex per dose at dose levels of 53.60 and 107.20 g/kg. Mortalities occurred as follows- males: 1/10, 0/10, respectively; females: 1/10, 1/10, respectively. Water diarrhea was observed in all animals beginning 15-20 minutes after dosing with hair around the anus markedly soiled. At 24 hours, soft yellowish stools and anal prolapse were observed in some animals; abdominal swelling, piloerection, facial edema, and soiling of hair over the entire body were also observed. Diarrhea ceased 48 hours after dosing. Necropsy revealed no treatment-related abnormalities. LD₅₀ (M/F) > 107.20 g/kg. NOEL not determined.

002; 068280; "Report on Acute Toxicity Study of MTI-500 (Etofenprox) in Rats" (Hashimoto, K., Hatano Research Institute, FDSC, Hatano, Kanagawa, Japan, Project No. A-82-27~34, 10/21/82). 811. MTI-500 (Lot # ST-101, purity = 96%), warmed in a water bath and administered as a singleavage dose to 10 Sprague-Dawley rats per sex per dose at dose levels of 21.44 and 42.88 g/kg. No mortalities occurred. Piloerection and crouching (immediately after dosing) reduced spontaneous movements, glossy stools or diarrhea, blood-like substance on eyelids or nostrils, and soiled hair were observed. Necropsy revealed scattered hemorrhagic points over the lungs of all animals, congested liver, and discoloration of the renal cortex. LD₅₀ (M/F) > 42.88 g/kg. NOEL not determined. Toxicity Category IV. Acceptable. (Corlett, 11/4/02)

Acute Oral Toxicity

Acute Oral Toxicity LD ₅₀	Acute Inhalation Toxicity LC ₅₀	Primary Eye Irritation	Primary Dermal Irritation	Dermal Sensitizer
IV	III	IV	IV	IV
Unacceptable but possibly upgradeable	Unacceptable			
Not a sensitizer				

Toxicity Category

ACUTE STUDIES - Technical

Submitted for manufacturing use only. Etofenprox is also known as MTI-500.

SUMMARY ("One-liners" from each study worksheet, significant information not mentioned in worksheets, other pertinent information for ongoing review or registration. Attach additional sheets if needed):

Active Ingredient: Etofenprox
 Formulated Product Name: Etofenprox Technical
 Formulation (excluding inert): 97% Etofenprox, 3% inert
 Chemical Code #: 2292
 EPA Reg. #: 33657-6
 Document #: 51626-002, -005 to -013, and -016 to -020, -023
 Company Name: Mitsui Chemicals, Inc.

DATA PACKAGE SUMMARY AND RECOMMENDATION SHEET - NEW ACTIVE INGREDIENT

FROM: Medical Toxicology Branch
 7/28/03

TO: Steve Rhodes, Registration Specialist
 Pesticide Registration Branch

Acute Dermal Toxicity

002; 068280; "Report on Acute Toxicity Study of MTI-500 (Ethofenprox) in Rats" (Hashimoto, K., Hatano Research Institute, FDSC, Hatano, Kanagawa, Japan, Project No. A-82-27~34, 10/21/82). 812. MTI-500 (Lot # ST-102, purity = 96%), warmed in a water bath and applied to the clipped skin of 10 Sprague-Dawley rats per sex per dose at a dose level of 2.144 g/kg for 24 hours. No mortalities occurred. Crouching and a reduction in spontaneous movement were observed in all animals 1 or 2 hours after application. Necropsy revealed no treatment-related abnormalities. Reported LD₅₀ (M/F) > 2.144 g/kg. Toxicity Category not determined. **Unacceptable but possibly upgradable** with submission of information detailing how the test article was held in contact with the skin during the exposure period. (Corlett, 11/4/02)

002; 068281; "Report on Acute Toxicity Study of MTI-500 (Ethofenprox) in Mice" (Hashimoto, K., Hatano Research Institute, FDSC, Hatano, Kanagawa, Japan, Project No. A-82-35~42, 10/21/82). 812. MTI-500 (Lot # ST-102, purity = 96%), warmed in a water bath and applied to the clipped skin of 10 ICR mice per sex per dose at dose levels of 1.072 and 2.144 g/kg for 24 hours. No mortalities occurred. No clinical signs were observed. Necropsy revealed no treatment-related abnormalities. Reported LD₅₀ (M/F) > 2.144 g/kg. Toxicity Category not determined. **Unacceptable but possibly upgradable** with submission of information detailing how the test article was held in contact with the skin during the exposure period. (Corlett, 11/4/02)

51626-0023; 205045; "Acute Dermal Toxicity Study of Etofenprox in Rats"; (S. Oda; Bozo Research Center, Inc., Gotemba Laboratory, Setagaya-ku, Tokyo 156-0042, Japan; Project ID. B-5040; 2/5/03); The skin of five Sprague-Dawley (Crj:CD(SD)IGS) rats/sex was treated with 0 or 2000 mg/kg of etofenprox technical (lot. no. 20024, purity: 99.0%) for 24 hours under an occlusive wrap. No deaths resulted from the treatment. No treatment-related clinical signs were evident. In the necropsy examination, no treatment-related lesions were noted. LD₅₀ (M/F) > 2000 mg/kg; Toxicity Category III; **Study acceptable.** (Moore, 7/25/03)

Acute Inhalation Toxicity

002; 068282; "MTI-500 Acute Inhalation Toxicity in Rats 4 Hour Exposure" (Jackson, G.C. et al., Huntingdon Research Centre, Huntingdon, Cambridgeshire, England, HRC Report No. MTC 60/821079, 4/2/86 (re-issue)). 813. MTI-500 (Lot No. ST-101, purity = 96%) was blended with acetone, aerosolized, and administered in a whole body manner to 5 COBS® rats per sex at a dose level (reported mean analytical concentration) of 5.9 mg/l (95% of the test material < 5.5 µm aerodynamic diameter) for 4 hours. No mortalities occurred. Treatment-related clinical signs included closing or partial closing of eyes and dyspnea during exposure, and oily fur, lethargy, hair loss (females only), and hyperactivity during the 14 day observation period. Necropsy revealed no treatment-related abnormalities except for a black area on the liver of 1 male. Reported LC₅₀ (M/F) > 5.9 mg/l. Toxicity Category not determined. **Unacceptable but possibly upgradable** with a clarification on the amount of acetone blended with the test material and the submission of the data and calculations used to determine the mean analytical concentration of the test material (Corlett, 10/10/02)

Primary Eye Irritation

002; 068285; "MTI-500 Primary Ophthalmic Stimulation Test in Rabbits" (Kashima, M., Haruna Laboratory, Nippon Experimental Medical Research Institute, Ltd., Agatsuma-gun, Gunma Prefecture, Japan, Project No. Nemri-H-85-55, 10/24/85). 814. 0.1 ml of MTI-500 (Lot No. ST-103, purity = 96.3%) was placed into the conjunctival sac of 1 eye of each of 6 Japanese White rabbits. No corneal opacity or iritis was observed in any treated eye. Grade 1 conjunctival irritation was observed in 5 of 6 treated eyes 24 hours after treatment with all signs of conjunctival irritation clearing in all treated eyes 72 hours after treatment. Toxicity Category IV. **Acceptable.** (Corlett, 10/25/02)

002; 068281; "Report on Acute Toxicity Study of MTI-500 (Ethofenprox) in Mice" (Hashimoto, K., Hatano Research Institute, FDS, Kanagawa, Japan, Project No. A-82-35-42, 10/21/82). MTI-500 (Lot # ST-101, purity = 96%), warmed in a water bath and administered at levels of 26.80 and 53.60 g/kg and observed for 14 days. No mortalities occurred. Swelling subcutaneously into the interscapular region of the dorsum of 10 ICR mice per sex per dose at the test site (in all animals) and swelling of the hair at the test site (in some animals at 53.60 g/kg) were observed. Histopathological examination revealed retention of test material at the test site and granuloma formation in the subcutaneous connective tissues at the test site. LD₅₀ (M/F) > 53.60 g/kg. NOEL not determined. **Supplemental study** (not a guideline study) (Cohett, 11/4/02)

002; 068280; "Report on Acute Toxicity Study of MTI-500 (Ethofenprox) in Rats" (Hashimoto, K., Hatano Research Institute, FDS, Kanagawa, Japan, Project No. A-82-27-34, 10/21/82). MTI-500 (Lot # ST-101, purity = 96%), warmed in a water bath and administered into the dorsal neck of 10 Sprague-Dawley rats per sex per dose at dose levels of 16.08 and 32.16 g/kg and observed for 14 days. No mortalities occurred. Piloerection, transient fluctuations in the frequency of respiration, and crouching were observed immediately after dosing at both 16.08, and 32.16 g/kg. At 32.16 g/kg, the injection site was markedly swollen with test article leakage in some animals. A blood-like substance on the eyelids or nostrils and grayish-white soft stools, swelling of the dorsal neck, and edema over the dorsal neck down to the forelegs were observed in all animals, along with hair soiled by oily dirt and scar formation or depilation at the injection site in some animals. Histopathological examination revealed retention of pale yellow viscous liquid and granulation tissues formed around the fluid in the subcutaneous tissue of the dorsal neck down to the forelegs with formation of granuloma in the subcutaneous connective tissues and congestion of the liver. LD₅₀ (M/F) > 32.16 g/kg. NOEL not determined.

SUPPLEMENTAL

002; 068283; "MTI-500 Skin Sensitization Test in Guinea Pigs" (Kobayashi, K., Oizumi Laboratory, Nippon Experimental Medical Research Institute, Ltd., Ohra-gun, Gunma Prefecture, Japan, no study or project number provided, 10/31/85). A modification of the Magnusson and Kligman maximization assay was used to assess the potential of MTI-500 (Lot No. ST-103, purity = 96.3%) to elicit delayed contact hypersensitivity in the guinea pig. 20 English Harlequin guinea pigs were treated with the test material during the challenge phase (intradermal injections followed 7 days later by a topical application) and during the challenge (topical application followed 7 days later by a topical application) and during the challenge (topical application 14 days following the topical induction dose). A concurrent negative control group consisting of 20 animals was also included in the study. The control animals were treated identically to the test animals except that during induction the test material was replaced with vehicle. Observations 48, and 72 hours after the challenge indicated that the test material was replaced with vehicle. Positive controls (uncontrolled) and negative dose did not indicate any skin-sensitization reaction. MTI-500 (Lot # ST-101, purity = 96%), warmed in a water bath and administered subcutaneously into the back of 10 Sprague-Dawley rats per sex per dose at dose levels of 16.08 and 32.16 g/kg and observed for 14 days. No mortalities occurred. Piloerection, transient fluctuations in the frequency of respiration, and crouching were observed immediately after dosing at both 16.08, and 32.16 g/kg. At 32.16 g/kg, the injection site was markedly swollen with test article leakage in some animals. A blood-like substance on the eyelids or nostrils and grayish-white soft stools, swelling of the dorsal neck, and edema over the dorsal neck down to the forelegs were observed in all animals, along with hair soiled by oily dirt and scar formation or depilation at the injection site in some animals. Histopathological examination revealed retention of pale yellow viscous liquid and granulation tissues formed around the fluid in the subcutaneous tissue of the dorsal neck down to the forelegs with formation of granuloma in the subcutaneous connective tissues and congestion of the liver. LD₅₀ (M/F) > 32.16 g/kg. NOEL not determined.

Dermal Sensitization

002; 068284; "MTI-500 Primarily Skin Stimulation Test in Rabbits" (Kashima, M., Haruna Laboratory, Nippon Experimental Medical Research Institute, Ltd., Agatsuma-gun, Gunma Prefecture, Japan, Project No. Nemri-H-85-5, 8/23/85). 815.5 ml (sic) of MTI-500 (Lot No. ST-103, purity = 96.3%) was applied to the clipped and shaved skin of the back of each of 6 Japanese white rabbits for 4 hours using a semi-occlusive wrap. No edema was observed at any test site. Grade 1 erythema was first observed in 1 animal 48 hours after patch removal. Persistence through 7 days after patch removal and clearing 8 days after patch removal. Toxicity Category IV. **Acceptable**. (Cohett, 10/24/02)

002; 068280; "Report on Acute Toxicity Study of MTI-500 (Ethofenprox) in Rats" (Hashimoto, K., Hatano Research Institute, FDSC, Hatano, Kanagawa, Japan, Project No. A-82-27~34, 10/21/82). MTI-500 (Lot # ST-101, purity = 96%), warmed in a water bath and administered intraperitoneally to 10 Sprague-Dawley rats per sex per dose at dose levels of 21.44 and 42.88 g/kg and observed for 14 days. No mortalities occurred. Piloerection and crouching with hollowed belly were observed immediately after dosing at both 21.44 and 42.88 g/kg. Diarrhea or soft stools were observed in all animals the day after test article administration. Necropsy revealed whitish yellow granules adhering to various organs in the abdomen including the fat tissue of the abdominal wall, omentum and mesenterium and around the testes in all animals; hemorrhagic points scattered in the lungs, congestion of the liver, and minor granuloma on the serous membrane of the liver and spleen and on the parietal peritoneum were also observed. LD₅₀ (M/F) > 42.88 g/kg. NOEL not determined. **Supplemental study** (not a guideline study) (Corlett, 11/4/02)

002; 068281; "Report on Acute Toxicity Study of MTI-500 (Ethofenprox) in Mice" (Hashimoto, K., Hatano Research Institute, FDSC, Hatano, Kanagawa, Japan, Project No. A-82-35~42, 10/21/82). MTI-500 (Lot # ST-102, purity = 96%), warmed in a water bath and administered intraperitoneally to 10 ICR mice per sex per dose at dose levels of 6.70, 13.40, 26.80, and 53.60 g/kg and observed for 21 days. Mortalities occurred as follows- males: 2/10, 3/10, 4/10, 3/10, respectively; females: 0/10, 1/10, 7/10, 7/10, respectively. 15 minutes after dosing, reduced appetite and reduced spontaneous movements were observed at all dose levels. 1 day after dosing, piloerection, facial edema, abdominal swelling, and soft stools were observed. Histopathological examination revealed the formation of minor granuloma in the serous membranes of liver, spleen, pancreas, and digestive tract. LD₅₀ (M/F) not determined. NOEL not determined. **Supplemental study** (not a guideline study) (Corlett, 11/4/02)

ACUTE STUDIES - Zoecon F254-87-1 Aerosol

	Toxicity Category
Acute Oral Toxicity LD50	IV
Acute Dermal Toxicity LD50	III
Acute Inhalation Toxicity LC50	IV
Primary Eye Irritation	IV
Primary Dermal Irritation	III
Dermal Sensitization	Not a sensitizer

Acute Oral Toxicity

002; 068288; "Acute Oral Toxicity Study in Rats Administered Test Article Zoecon F254-87-1 Aerosol, Lot No. L255-140-1" (Davis, T.K., UBTL, Inc., Salt Lake City, UT, Study #63296, 5/8/87). 811. Zoecon F254-87-1 Aerosol (Lot No. L255-140-1, 1.3% etofenprox, 0.38% (S)-hydropropene) was administered as a single gavage dose to 5 Sprague Dawley rats per sex per dose at a dose level of 5.1 g/kg. No mortalities occurred. Nasal discharge was observed in 2 animals on the day of dosing clearing in both animals on the next day. Necropsy revealed kidneys exhibiting light red to dark red mottled appearance in 1/5 males and in 2/5 females and each kidney exhibiting 2-12 infarcts in 3/5 males and 3/5 females. LD₅₀ (M/F) > 5.1 g/kg. Toxicity Category IV.

Acceptable. (Corlett, 10/30/02)

Acute Dermal Toxicity

002; 068287; "Acute Dermal Toxicity Study in Rabbits Administered Test Article Zoecon F254-87-1 Aerosol, Lot No. L255-140-1" (Davis, T.K., UBTL, Inc., Salt Lake City, UT, Study #63297, 5/8/87). 812. Zoecon F254-87-1 Aerosol (Lot No. L255-140-1, 1.3% etofenprox, 0.38% (S)-hydropropene) was applied to the clipped skin of 5 New Zealand White rabbits per sex per dose at a dose level of 2.1 g/kg for 24 hours. No mortalities occurred. No treatment-related clinical signs were observed. Erythema was observed in all animals after patch removal; edema and eschar were also observed in some animals. Necropsy revealed dry skin at the exposure site in 1 male

Acute Inhalation Toxicity

002; 068286; "The Acute Toxicity of Inhaled Zoecon F254-87-1 Aerosol (Lot No. L255-140-1 and L255-149-1) in the Albino Rat (Safety Test)" (Vial, A. et al., Bio-Research Laboratory Ltd., Sennerville, Quebec, Canada, Project No. 82969, 6/8/87). 813. F254-87-1 Aerosol (Lot No. L255-140-1 and L255-149-1, 1.3% etofenprox, 0.4% (S)-hydroprene) was aerosolized and administered in a whole body manner to 5 Crl:CD[®](SD)BR rats per sex at a dose level (mean gravimetric concentration) of 4.32 mg/l (mean mass median particle diameter (GSD) of 3.5 (2.0) μ m) for 4 hours. No mortalities occurred. Treatment-related clinical signs included partial closing of eyes, inactivity, and slightly wet fur after exposure, and red muzzle staining, pale eye color, dizziness, and rough and wet fur after exposure, all signs cleared the next day. Necropsy revealed no treatment-related abnormalities. LC_{50} (M/F) > 4.32 mg/l. Toxicity Category IV. Acceptable.

(Corlett, 10/29/02)

Primary Eye Irritation

002; 068289; "Primary Eye Irritation Study in Rabbits Administered Test Article Zoecon F254-87-1 Aerosol, Lot No. L255-140-1" (Davis, T.K., UBTL, Inc., Salt Lake City, UT, Study #63299, 5/8/87). 814. A single 1 second burst from a distance of approximately 10 cm of Zoecon F254-87-1 Aerosol (Lot No. L255-140-1, 1.3% etofenprox, 0.38% (S)-hydroprene) was administered to 9 New Zealand white rabbits. 3 of the treated eyes were washed and 6 were not washed. No corneal opacity or irritation was observed in any unwashed treated eye. Grade 1 eye of each of 9 New Zealand white rabbits. 3 of the treated eyes were washed and 6 were not washed. No conjunctival irritation was observed in 3 of 6 unwashed treated eyes 1 hour after treatment with all etofenprox, 0.38% (S)-hydrorene. Grade 2 erythema was observed in all animals 24 and 72 hours Zealand rabbits for 4 hours. Grade 2 erythema was observed in all animals 24 and 72 etofenprox, 0.38% (S)-hydrorene) was applied to each of 2 sites on the clipped skin of each of 6 New Zealand rabbits for 4 hours. Grade 2 erythema was observed in all animals 24 and 72 hours after patch removal, decreasing to grade 1 in 2 animals and grade 1 in 4 animals 7 days after patch removal, and decreasing to grade 1 in 3 animals 14 days after patch removal. Grade 1 edema was observed in 3 animals 24 hours after patch removal and in 1 animal 72 hours after patch removal with all signs of edema clearing in all animals 7 days after patch removal. Toxicity Category III. Acceptable. (Corlett, 10/31/02)

Dermal Sensitization

002; 068290; "Dermal Sensitization Study in Albino Guinea Pigs Administered Test Article Zoecon F254-87-1 Aerosol, Lot No. L255-140-1" (Davis, T.K., UBTL, Inc., Salt Lake City, UT, Study #63300, 5/8/87). 816. A modified version of the Buehler method was used to assess the skin sensitization potential of Zoecon F254-87-1 Aerosol (Lot No. L255-140-1, 1.3% etofenprox, 0.38% (S)-hydrorene). 10 Hartley albino guinea pigs were treated with the test material placed on a shaved area for 6 hours, 1 application per week for 3 weeks (3 total applications). Each animal was then challenged with the same induction dose at a naïve site on each animal, 2 weeks following the third induction dose, for 6 hours. The test material produced a positive result in 20% of the treated animals 48 hours after challenge application. Positive controls functional.

The results of this study indicate that the test material is a potent contact sensitizer when using this modified version of the method of Buehler. Acceptable. (Corlett, 11/4/02)

002; 068291; "Primary Dermal Irritation Study in Rabbits Administered Test Article Zoecon F254-87-1 Aerosol, Lot No. L255-140-1" (Davis, T.K., UBTL, Inc., Salt Lake City, UT, Study #63291, 5/8/87). 817. 0.5 ml of Zoecon F254-87-1 Aerosol (Lot No. L255-140-1, 1.3% etofenprox, 0.38% (S)-hydrorene) was applied to each of 2 sites on the clipped skin of each of 6 New Zealand rabbits for 4 hours. Grade 2 erythema was observed in all animals 24 and 72 hours after patch removal, decreasing to grade 1 in 2 animals and grade 1 in 4 animals 7 days after patch removal, and decreasing to grade 1 in 3 animals 14 days after patch removal. Grade 1 edema was observed in 3 animals 24 hours after patch removal and in 1 animal 72 hours after patch removal with all signs of edema clearing in all animals 7 days after patch removal. Toxicity Category III. Acceptable. (Corlett, 10/31/02)

002; 068292; "Dermal Sensitization Study in Albino Guinea Pigs Administered Test Article Zoecon F254-87-1 Aerosol, Lot No. L255-140-1" (Davis, T.K., UBTL, Inc., Salt Lake City, UT, Study #63301, 5/8/87). 818. A modified version of the Buehler method was used to assess the skin sensitization potential of Zoecon F254-87-1 Aerosol (Lot No. L255-140-1, 1.3% etofenprox, 0.38% (S)-hydrorene). 10 Hartley albino guinea pigs were treated with the test material placed on a shaved area for 6 hours, 1 application per week for 3 weeks (3 total applications).

Each animal was then challenged with the same induction dose at a naïve site on each animal, 2 weeks following the third induction dose, for 6 hours. The test material produced a positive result in 20% of the treated animals 48 hours after challenge application. Positive controls functional.

The results of this study indicate that the test material is a potent contact sensitizer when using this modified version of the method of Buehler. Acceptable. (Corlett, 11/4/02)

SUBCHRONIC STUDIES

(Oral)

007; 186424; "Assessment of the Toxicity of MTI-500 in Rats by Dietary Administration for 13 Weeks" (Green, O.P. et al., Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, England, Laboratory Project ID MTC 56/821067/2, 4/2/86). 821. MTI-500 (Batch No. ST-101, purity = 96%) was admixed to the diet and fed to 20 CD rats per sex per dose at dose levels of 0 (diet and corn oil only), 50, 300, 1800, or 10800 ppm (0, 3.3, 20, 120, 734 mg/kg/day, respectively, for males and 0, 3.8, 23, 142, 820 mg/kg/day, respectively, for females) for 13 weeks. No treatment-related mortalities occurred. No treatment-related clinical signs were observed. A treatment-related decrease in mean thyroxine (T_4) levels in males at 1800 and 10800 ppm was observed. Treatment-related increases in mean adjusted liver weight in males at 10800 ppm and in females at 1800 and 10800 ppm and mean adjusted thyroid weight in males at 1800 and 10800 ppm were observed. Microscopic examination revealed an increased incidence of microfollicles in the thyroid in males at 1800 and 10800 ppm and in females at 10800 ppm and enlargement of the centrilobular hepatocytes in females at 10800 ppm. **No adverse effects.** NOEL (M) = 20 mg/kg/day (300 ppm) based on an increased incidence of microfollicles in the thyroid, NOEL (F) = 23 mg/kg/day (300 ppm) based on increased liver weights and enlargement of the centrilobular hepatocytes. **Acceptable.** (Corlett, 11/22/02)

006; 186423; "Assessment of the Toxicity of MTI-500 to Mice by Dietary Administration for 13 Weeks" (Green, O.P. et al., Huntingdon Research Centre plc, Huntingdon, Cambridgeshire, England, Laboratory Project ID MTC 55/821112/2, 4/2/86). 821. MTI-500 (Batch No. ST-103, purity = 96%) was admixed to the diet and fed to 20 CD-1 mice per sex per dose at dose levels of 0 (diet and corn oil only), 50, 500, 3000, or 15000 ppm (0, 6.1, 60, 375, 1975 mg/kg/day, respectively, for males and 0, 6.9, 71, 390, 2192 mg/kg/day, respectively, for females) for 13 weeks. 2 males and 6 females at 15000 ppm died or were killed for humane reasons and these deaths are considered treatment-related. At 15000 ppm, treatment-related piloerection, hunched posture, emaciated and/or anemic appearance, body tremors, and respiratory distress in both sexes, and lethargy and unsteady gait in females were observed. Treatment-related decreased body weight gain and increased water consumption were observed in both sexes at 15000 ppm. Treatment-related increases in mean urea nitrogen and cholesterol levels and in mean relative liver and kidney weights were observed in both sexes at 15000 ppm. Macroscopic examination revealed kidneys that were pale, enlarged, and with cortical scarring in both sexes at 15000 ppm. Microscopic examination revealed kidneys with widespread tubular basophilia, extensive tubular dilatation, and dilatation of the renal pelvis, centrilobular hepatocyte enlargement, increased cellularity of splenic white pulp, and lymphoid hyperplasia in both sexes at 15000 ppm. **No adverse effects.** NOEL (M) = 375 mg/kg/day (3000 ppm), NOEL (F) = 390 mg/kg/day (3000 ppm) based on kidneys with widespread tubular basophilia and extensive tubular dilatation. **Acceptable.** (Corlett, 11/18/02)

(Dermal)

008; 186425; "A 28-Day Repeated Dose Dermal Toxicity Study in Rabbits with Technical MTI-500" (Killeen, J.C., Jr., Toxicology & Metabolism, Ricerca, LLC, Painesville, OH, Document No. 011077-1, 6/28/00). 870.32. Technical MTI-500 (Lot No. 21049, purity = 99.18%) was applied to the clipped dorsal skin of 10 New Zealand White rabbits per sex per dose at dose levels of 0 (tap water only), 400, 650, or 1000 mg/kg/day for 6 hours per day, for 28 consecutive days. In addition, 10 animals per sex at the control and high dose levels were used to assess recovery (recovery group animals were observed for an additional 2 weeks after the others were sacrificed). No mortalities occurred. No treatment-related systemic clinical signs were observed. Body weight and organ weight determinations along with hematology and serum chemistry revealed no treatment-related effects. Treatment-related erythema at the test site was observed at the 400, 650 and 1000 mg/kg/day dose levels in both sexes throughout the 28-day treatment period. Microscopic examination revealed treated skin where the epidermis exhibited treatment-related diffuse hyperplasia at 400, 650, and 1000 mg/kg/day in both sexes; treated recovery group animals did not significantly exhibit this effect. **No adverse effects.** NOEL (M/F, systemic) = 1000 mg/kg/day based on no treatment-related effects at the highest dose tested; NOEL (M/F,

**51626-020 186461, "The Biokinetics and Metabolism of ^{14}C -Ethofenprox in the Rat", (D. R. Hawkins, et al., Department of Chemical Metabolism and Radiosynthesis, Huntingdon Research Centre, Huntingdon, Cambridgeshire, England, HRC Report No. MTC 68/84610, 1 August 1985).

Plasma concentrations of radioactivity were found in the liver (range 3.1 to 9.6 $\mu\text{g/g}$). Whole liver animals, contained very high radioactivity levels. Acceptable. (Green and Gee, 4/10/03). Found in kidneys and fat. Lowest concentrations were in muscle. Next highest concentrations were contained between 0.25% and 0.91% dose in the four animals. Next highest concentrations were concentrations of radioactivity were found in the liver (range 3.1 to 9.6 $\mu\text{g/g}$). Whole liver plasma concentrations peaked from 15 minutes to 3 hours after dosing at 4.43 to 7.16 $\mu\text{g/ml}$. Extracted radioactivity, equivalent to 3.5% and 2.9% of the administered dose respectively. Phenoxyl moiety of ethofenprox. They accounted for 6.1% (male) and 4.6% (female) of the ethylidene of the ethoxyphenyl moiety, and, the other, from aromatic ring-hydroxylation of the respecitively. The next most plentiful components in feces were 2 metabolites, one from O-deethofenprox accounting for 91.4% and 93.3% of the radioactivity extracted from feces (0-24 hours post-dosing) of males and females respectively. The radioactivity in feces was 48.5% and 59% of the dose dose in 5 days of which 5.0% was eliminated within 24 hours after treatment. Unchanged dosing. Excretion of radioactivity in urine (including cage wash) accounted for a mean of 6.2% of during the first 24 hours. 89.5% (mean of 4 animals) was excreted during the five days after radiotoxicity was excreted mainly in the feces. 86.7% of the dose was excreted in the feces. Two Beagle dogs per sex received a single oralavage dose of ^{14}C -Ethofenprox at 30 mg/kg. Huntingdon, Cambridgeshire, England, HRC/MTC 69/84583, 11 October 1985).

Department of Chemical Metabolism and Radiosynthesis, Huntingdon Research Centre, Huntingdon, Cambridgeshire, England, HRC Report No. HRC/MTC 69/84583, 11 October 1985).

**51626-020 186460, "The Metabolism of ^{14}C -Ethofenprox in Dogs", (D. R. Hawkins, et al.,

METABOLISM STUDIES

Mean analytical concentrations of the test material. (Cohett, 12/3/02)

upgradable with the submission of the data and calculations used to determine the reported together with adrenals with a minimally increased cortical width. Unacceptable but possibly thyroid; NOEL (F) = 0.042 mg/l based on enlarged adrenals and increased adrenal weight increased number of microfollicles and minimally increased height of follicular epithelium in the thyroid in males at 1.01 mg/l and a minimally increased corticomedullar hepatocytes and 0.21 and 1.01 mg/l. No adverse effects. NOEL (M) = 0.21 mg/l based on increased liver and increased number of microfollicles and a minimally increased height of follicular epithelium in the thyroid weight together a minimally enlarged corticomedullar hepatocytes and a minimally increased adrenal weight in females at 0.21 and 1.01 mg/l. Microscopic examination revealed minimal enlargement of centrilobular hepatocytes in both sexes at 1.01 mg/l, a minimally increased number of enlarged adrenals in females at 0.21 and 1.01 mg/l were observed. Macroscopic examination mean adrenal weight in females at 0.21 and 1.01 mg/l revealed. Treatment-related scab formation at the back of the ears was observed in males at 1.01 mg/l and in females at 0.21 and 1.01 mg/l. Treatment-related increases in mean liver and thyroid weights in both sexes at 1.01 mg/l and revealed enlarged adrenals in females at 0.21 and 1.01 mg/l. Microscopic examination revealed mean adrenal weight in females at 0.21 and 1.01 mg/l were observed. Treatment-related scab formation week for 13 consecutive weeks. No mortalities were reported. Treatment-related scab formation of the test material < 5.5 μm equivalent aerodynamic diameter) for 6 hours per day 6 days per concentration at the high dose level), 0.042, 0.21, 1.01 mg/l (with an average of 90.1% to 90.9% whole-body manner to 15 Wistar rats per sex per dose levels (reported mean analytical concentration) of 0 (air control), 0 (acetone only), at a concentration equal to the acetone week for 13 consecutive weeks. No mortalities were reported. Treatment-related scab formation was mixed with acetone (90% test article:10% acetone, w/w), aerosolized, and administered in a MTC 81/841257, 8/23/85). 824, Ethofenprox (MTI-500, Batch No. ST 103, Purity = 96%) Huntingdon Research Ltd, Huntingdon, Cambridgeshire, England, Laboratory Project ID 009; 186426; "Ethofenprox (MTI-500) 90-Day Inhalation Study in Rats" (Coombs, D.W. et al., (inhalation)

Acceptable. (Cohett, 12/1/02)

skin) < 400 mg/kg/day based on incidences of erythema and epidermis with diffuse hyperplasia.

Single (30 and 180 mg/kg) and multiple (30 mg/kg/day for 7 or 14 consecutive days) doses of ¹⁴C-ethofenprox were used for groups of 3, 5, or 25 CD rats per sex or 3 or 10 pregnant/lactating females per group to evaluate metabolic and pharmacokinetic parameters.

A single oral dose of ¹⁴C-ethofenprox at 30 mg/kg to 5 rats per sex was mainly eliminated in the feces. During the 5 days following dosing, means of 88.0% and 86.4% dose were excreted by males and females respectively by this route. Approximately equal amounts (35% to 40% of dose) were excreted by both sexes during the 0 to 24 hour and 24 to 48 hour periods. Excretion of radioactivity in the urine accounted for means of 10.8% (males) and 8.0% (females) over 5 days and most was excreted in the first 24 hours. Mean total retention of radioactivity in the bodies 5 days post-dosing was 3.4% (males) and 3.5% (females). The pattern of excretion of radioactivity after a single oral dose of ¹⁴C-ethofenprox to 5 per sex at 180 mg/kg was similar to that seen at 30 mg/kg. Tissue concentrations of radioactivity were measured at 120 hours after dosing. Highest mean tissue concentrations were found in fat of 30 mg/kg dosed animals (16.6 µg/g in males, 11.1 µg/g in females). Muscle concentrations were near the limit of accurate measurement (0.05 µg/g). Liver contained mean concentrations of 0.34 µg/g (males) and 0.33 µg/g (females). Mean kidney concentrations were 0.13 and 0.16 µg/g for males and females respectively. At 180 mg/kg, mean fat concentrations of radioactivity were 90.2 µg/g and 94.0 µg/g for males and females respectively 120 hours after dosing. Concentrations in other tissues were all below 2 µg/g. Unchanged ethofenprox accounted for 6.6% and 14.0% of dose for males and females respectively at 30 mg/kg, and, for 22.6% and 29.0% respectively at 180 mg/kg in extracts of rat feces collected during 72 hours. The metabolite desethylethofenprox was 19.5% (males) and 25.1% (females) at 30 mg/kg and 23.2% and 20.6% respectively at 180 mg/kg over the same time period. Another metabolite, 4'-hydroxyethofenprox, made up 13.2% and 13.8% at 30 mg/kg and 7.2% and 8.1% at 180 mg/kg of the extracts for males and females respectively.

After a single oral dose at 30 mg/kg to 5 per sex, peak plasma concentrations (approximately 5 µg/ml) occurred 2 to 7 hours later. Peak plasma concentrations (16 µg/ml to 17 µg/ml) were reached 5 hours post-dosing after a single dose of 180 mg/kg.

In a tissue distribution assay, 30 mg/kg/day of ¹⁴C-ethofenprox was administered to 25 rats per sex on seven consecutive days. 5 per sex were sacrificed for sampling at 4, 24, 48, 120, and 240 hours after the last dose. The highest concentrations of radioactivity in all tissues were found at 4 hours post-dosing. Fat contained the highest concentration (94.2 µg/g to 101 µg/g). Next highest concentrations (30.5 µg/g male, 22.3 µg/g female) were found in liver at 4 hours. The major component in fat and liver was unchanged ethofenprox.

10 pregnant female rats received 30 mg/kg/day of ¹⁴C-ethofenprox by oral intubation on gestation days 10 through 16. 2 dams were sacrificed for sampling at 4, 24, 48, 72, and 120 hours after the last dose. Adrenal glands, kidneys, heart, and liver showed radioactivity concentrations and patterns of elimination of radioactivity similar to non-pregnant animals. Of those, adrenal glands contained the highest concentrations, 61.5 µg/g at 4 hours, declining to 5.74 µg/g at 120 hours. Of the reproductive tissues, mammary contained the highest concentrations (87.4 µg/g at 4 hours declining to 32.4 µg/g at 120 hours after the last dose), similar to those in fat of non-pregnant animals. Radioactivity concentrations in placentae were lower than in any other maternal tissue. Concentrations declined from 4.6 µg/g to 4.8 µg/g at 4 hours to 0.17 µg/g at 120 hours. Maximum fetal concentrations were 1.6 µg/g to 1.7 µg/g at 4 hours.

Secretion of radioactivity into the milk of mother rats was evaluated by analysis of the stomach contents of suckling pups. Dams were treated with 30 mg/kg/day of ¹⁴C-ethofenprox by oral intubation from gestation day 18 through lactation day 9 (14 days total). Radioactivity concentration in pup stomach contents ranged from 41.3 µg/g to 88.3 µg/g after one hour of suckling compared to maternal plasma concentrations in the range of 1.9 µg/ml to 3.6 µg/ml. Chromatographic analysis indicated that 95% of the radioactivity ingested by the pups was associated with unchanged ethofenprox. **Acceptable.** (Green and Gee, 4/10/03).

51626-010 186427, "Ethofenprox (MTI-500) Toxicity to Dogs by Repeated Dietary Administration for 52 Weeks Followed by a Recovery Period of 8 Weeks", (Robert J. Halling, et al., Huntingdon Research Centre, Ltd., Huntingdon, Cambridgeshire, England, Report # MTI 71/85234, 25 October 1985). 6 (control and high dose) or 4 Beagle dogs per sex per group

Chronic Toxicity, Dog

Effects (% of bodyweight) were higher for 4900 ppm males at weeks 26 and 106 and for 700 ppm males at week 26. Relative liver weights were also increased. Absolute and relative thyroid weights were increased for 4900 ppm females at weeks 26 and 106 and for 700 ppm males at week 26 and for females at week 26 and for 700 and 4900 ppm males at week 52. Increased liver terminations. Absolute (with statistical significance) and relative kidney weights were increased for females at 4900 ppm. Enlarged thyroid was increased in 4900 ppm females at terminal sacrifice. Thyroid adenomas plus carcinomas were increased at 4900 ppm with a positive significant trend in males and a significant increase in females by pair wise comparison (0/50 versus 9/50). Non-neoplastic changes were observed as increased central lobular hepatocyte enlargement at 26 weeks and a significant increase in females by pair wise comparison (0/50 versus 9/50). Non-neoplastic liver changes in main group animals at 700 and 4900 ppm. Chronic NOEL = 100 ppm (non-sacrifice (satellite) and at termination (main) in 4900 ppm animals and as increases in eosinophilic hepatocytes in main group animals at 700 and food consumption). Possible adverse effects (thyroid tumors at 4900 ppm). 186439 is a photomicrography addendum for histopathology. Acceptable. (Green and Gee, 4/3/03).

SB950-MANDATED HEALTH EFFECTS STUDIES

**51626-011, 012 186428, 186439, "Ethofenprox (MTI-500) Potential Tumorigenic and Toxic Effects in Prolonged Dietary Administration to Rats (Final Report)", (Open P. Green, et al., Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, England, Report # MTI 59/85581, 24 January 1986). 70 CD rats per sex per group of Sprague-Dawley origin received ethofenprox (MTI 500) technically (96.3%) in the diet at 0 (corn oil + basal diet), 30, 100, 700, and 4900 ppm for 110 weeks. 50 and 20 animals per sex per group were designated male and satellite animals and for interim sacrifice after 26 and 52 weeks of treatment. Group mean mg/kg/day intervals and for 110 weeks of treatment. Satellite animals were used for blood and urine sampling at 4.8, 25.5 and 34.3; and 186.7 and 249.1 mg/kg/day for males and females respectively. 24% to 34% reductions in bodyweight gain were recorded for males and females respectively receiving 4900 ppm throughout the treatment period. Marginally lower water intake was noted for males and females receiving 4900 ppm during the treatment period. Statistical significant increases in absolute liver weight were recorded in both sexes at 5, 12, and 23. Statistically significant increases in relative liver weight were also recorded. Marginaly lower water intake was noted for males and females receiving 4900 ppm during the treatment period. Group mean mg/kg/day through week 26 and for females at weeks 26 and 106 and for 700 and 4900 ppm males at week 26 and for females at week 52, and 110. Absolute (with statistical significance) and relative thyroid weights were increased for 4900 ppm females at weeks 26 and 106 and for 700 ppm males at week 26 and for females at week 26 and for 700 and 4900 ppm males at week 52. Increased liver terminations. Absolute (with statistical significance) and relative kidney weights were increased for females at 4900 ppm. Enlarged thyroid was increased in 4900 ppm females at terminal sacrifice. Thyroid adenomas plus carcinomas were increased at 4900 ppm with a positive significant trend in males and a significant increase in females by pair wise comparison (0/50 versus 9/50). Non-neoplastic changes were observed as increased central lobular hepatocyte enlargement at 26 weeks and a significant increase in females by pair wise comparison (0/50 versus 9/50). Non-neoplastic liver changes in main group animals at 700 and 4900 ppm. Chronic NOEL = 100 ppm (non-sacrifice (satellite) and at termination (main) in 4900 ppm animals and as increases in eosinophilic hepatocytes in main group animals at 700 and food consumption). Possible adverse effects (thyroid tumors at 4900 ppm). 186439 is a photomicrography addendum for histopathology. Acceptable. (Green and Gee, 4/3/03).

received ethofenprox (MTI-500) (96.3% purity) in the diet at 0 (basal diet + corn oil), 100, 1000, and 10000 ppm for 52 weeks. In a recovery phase, 2 animals per sex from the control and high dose groups received untreated diet for 8 weeks following treatment. Mg/kg/day equivalents for males and females were 3.46 and 3.17; 33.37 and 32.19; and 351.73 and 339.32 at 100, 1000, and 10000 ppm respectively. Statistically significant decreases in total protein and cholesterol and increases in alkaline phosphatase were noted for 10000 ppm males and females from week 6 onwards. NOEL = Cannot be determined. After 52 weeks of treatment, lung, liver, kidney, and pancreas weights (as % of bodyweight) were increased (statistical significance for liver) for both sexes at 10000 ppm relative to controls. One 1000 ppm female and 2 males and 1 female at 10000 ppm were noted with accentuation of the lobular markings of the liver at 52 week necropsy. Histopathology revealed 2/4 female dogs at 10000 ppm with minimal swelling of centrilobular liver cells at 52 weeks. The noted changes were generally diminished or absent after the 8 week recovery period. **No adverse effects.** Unacceptable, upgradeable (with dose level justification). (Green and Gee, 4/10/03).

Oncogenicity, Mouse

**51626-013, 016 186440, 186443, "Ethofenprox (MTI-500) Potential Tumorigenic and Toxic Effects in Prolonged Dietary Administration to Mice (Final Report)", (Owen P. Green, et al., Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, England, Report # MTC 58/85582, 6 January 1986). Seventy-six CD-1 mice (of Swiss origin) per sex per group received ethofenprox (MTI-500) technical (96.3%) in the diet at 0 (basal diet + corn oil), 30, 100, 700, and 4900 ppm for 108 weeks. Fifty-two per sex per group, designated main group animals, were treated through 108 weeks. The remaining 24 per sex per group satellite animals were used for blood and urine sampling at intervals through week 52 and for interim necropsies at 26 and 52 weeks. Mean mg/kg/day intake of ethofenprox for weeks 1 through 108 was 3.1 and 3.6, 10.4 and 11.7, 75.2 and 80.9, and 546.9 and 615.5 mg/kg/day for males and females at 30, 100, 700, and 4900 ppm respectively. For males at 4900 ppm, survival was reduced at study termination and bodyweight gain was decreased through week 52. Water consumption increased (statistically significant) for both sexes at 4900 ppm for weeks 5, 12, and 23 and urine volume was higher (statistically significant) for males at all treatment levels at week 52. Absolute (g) liver weights were higher (statistically significant) for males at 4900 ppm and relative liver weights (% bodyweight) were increased for both sexes. Also at necropsy, in both sexes, the incidence of pale kidneys was increased at 100, 700, and 4900 ppm and renal cortical scarring incidence was higher at 4900 ppm. Treatment related non-neoplastic changes were confined to the kidney. Increases in dilated/basophilic cortical tubules of varying severity were noted for both sexes at 100, 700, and 4900 ppm and for males at 30 ppm. This lesion was associated with focal loss of tubules at the higher dose levels. No carcinogenicity, no adverse effects. Chronic NOEL = 30 ppm (3.1 and 3.6 mg/kg/day in males and females respectively) (kidney changes). Record 186443 contains a photomicrography addendum for kidney changes. No evidence of oncogenicity. Acceptable. (Green and Gee, 4/2/03).

The study (record 186441) discussed the U.S. EPA classification of etofenprox as a Group C Oncogen on the basis of increased incidence (outside the historical control range for the performing laboratory) of thyroid follicular cell adenomas and adenomas/carcinomas combined in the rat. The authors requested a reclassification for etofenprox to Group D or E Oncogen based on the negative results of mice and dog studies previously conducted showing no thyroid oncogenicity. Also, on results of the *in vitro* studies (non-guideline protocols) in the appendix on the *in vitro* based effect of etofenprox on FRTL 5 (Fischer rat thyroid follicular cells). The broadening of the historical control pool that included more data for the strain from the rat supplier indicated more variability for thyroid effects than in the initial evaluation. Record 186442 appendix contains full copies of published literature listed in the references of 186441. Publications in 186442 were not given a review. The argument was being made for a non-genotoxic mechanism for thyroid tumor induction and the use of a MOE. (Green and Gee, 4/03/03).

Reproductive, Rat
**51626-018 186473, "Effect of Ethofenprox (MTI-500) on Multiple Generations of the Rat", (David D. Cozens, et al., Huntingdon Research Centre, Ltd., Huntingdon, Cambridgeshire, England, Report No. MTC 67/85706, 9 October 1985). In the F0 generation, 28 Chi:COBS CD(SD)BR rats per sex per group received Ethofenprox (MTI-500) technical (96.3%) in the diet at 0 (SF Laboratory Animal Diet No. 2 + corn oil), 100, 700, and 4900 ppm starting 70 days pre-

thyroid weights were increased at 4900 ppm in both sexes. Necropsy showed an increase in thyroid weights 4-14 of treatment. Relative (% of body weight) F0, F1, and F2b liver, kidney, and F0 and F1b female body weights at 4900 ppm were lower (5% to 7%) than controls generally during weeks. F2b adults were reared to maturity. Water consumption was increased for F1a, F1b, F2 (F2b) animals. Twenty-four F1 (F1b) animals per sex per group were allowed to mate during 2 months. Twenty-four F1 (F1b) animals per sex per group were allowed to mate during 2 months. Water consumption was increased for F1a, F1b, F2 (F2b) animals. Necropsy showed an increase in thyroid weights at 4900 ppm in both sexes. Necropsy showed an increase in relative body weight of 5% to 7% in the kidneys in the F1b animals. Focal medullary fibrosis, mineral deposits, and necrosis of pyelonephritis was observed in some animals. Cortical scarring and an increased incidence of dilated cortical tubules or basophilic tubules in males was also noted. One F0 female was also noted with cystic collecting ducts. Some of these effects were not seen in F0 kidneys. In the liver, minimal centrilobular hepatocyte enlargement was recorded in both sexes at 4900 ppm. Thyroid changes were limited to minimal increased height of the follicular epithelium in males (6/23) at 4900 ppm. Although histopathology was not conducted on female rats received Ethofenprox (MTI-500) technical (96.3% purity) by average at 0 (1% methylcellulose), 12.5, 25, and 5000 mg/kg/day on gestation days 6 through 17, 21-24 per group were sacrificed on gestation day 20 for teratogenicity evaluation. Remaining females per group were all allowed to give birth and rear the offspring day 21. An F1 generation was selected from those pups to assess the reproductive effects of their previous exposure to ethofenprox. The untreated reproductive phase continued through weaning of the F2 generation. Teratogenicity phase results: Increased salivation was noted for dams at 250 and 5000 mg/kg/day. Weibrown staining around the mouth and wetgellow stained fur around the anogenital region were increased at 5000 mg/kg/day. The incidence of fetal visceral malformations was slightly higher at 5000 mg/kg/day. One fetus from each of 3 females was unaffected. 1 fetuses with microphthalmia, another with internal hydrocephaly and absent innominate artery, and a third with right microphthalmia and left anophthalmia were noted. The incidence was not statistically significant on a litter basis. Maternal NOEL = 250 mg/kg/day (increased wetbrown staining around the mouth and wetgellow stained fur around the anogenital region at 5000 mg/kg/day). Developmental NOEL = 5000 mg/kg/day. Reproductive

assessments: Time to vaginal opening was marginally earlier for F1 females (exposed in utero) relative to controls. In the hole-board test, F1 males and females in the 250 and 5000 mg/kg/day groups showed slightly lower mobility than controls. Resting counts were also lower for males in these groups. F1 females from all treatment groups also had slightly longer entry times on day 1 and 2 in the passive avoidance test. F2 generation litter results were generally in line with controls. Acceptable with no teratogenicity. (Green, Gee, and Leung 4/4/03). Females in these groups, F1 females from all treatment groups also had slightly longer entry times on day 1 and 2 in the passive avoidance test. F2 generation litter results were generally in line with controls. Acceptable with no teratogenicity. (Green, Gee, and Leung 4/4/03).

**51626-016 186444, "Effect of Ethofenprox (MTI-500) on Pregnancy of the Rat with Rearing to Maturity of the F1 Generation", (David D. Cozens, et al., Huntingdon Research Centre Ltd., England, Report # MTC 64/85422, 28 October 1985). 35 seminatal Chi:COBS CD (SD) BR rats received Ethofenprox (MTI-500) technical (96.3% purity) by average at 0 (1% methylcellulose), 12.5, 25, and 5000 mg/kg/day on gestation days 6 through 17, 21-24 per group were sacrificed on gestation day 20 for teratogenicity evaluation. Remaining females per group were all allowed to give birth and rear the offspring day 21. An F1 generation was selected from those pups to assess the reproductive effects of their previous exposure to ethofenprox. The untreated reproductive phase continued through weaning of the F2 generation. Teratogenicity phase results: Increased salivation was noted for dams at 250 and 5000 mg/kg/day. Weibrown staining around the mouth and wetgellow stained fur around the anogenital region were increased at 5000 mg/kg/day. The incidence of fetal visceral malformations was slightly higher at 5000 mg/kg/day. One fetus from each of 3 females was unaffected. 1 fetuses with microphthalmia, another with internal hydrocephaly and absent innominate artery, and a third with right microphthalmia, another with internal hydrocephaly and absent innominate artery, and a third with right microphthalmia and left anophthalmia were noted. The incidence was not statistically significant on a litter basis. Maternal NOEL = 250 mg/kg/day (increased wetbrown staining around the mouth and wetgellow stained fur around the anogenital region at 5000 mg/kg/day). Developmental NOEL = 5000 mg/kg/day. Reproductive

Teratology, Rat

Acceptable. (Green and Gee, 4/9/03).

= 700 ppm (lower pup weight and pup loss (days 12 to 21) at 4900 ppm). No adverse effects. 700 ppm (cystic collecting in kidneys at 4900 ppm). Reproductive NOEL = 4900 ppm. Pup NOEL = F0 reproductive organs/tissues, a thorough exam was done on the F1b adults. Parental NOEL = F0 reproductive epithelium in males (6/23) at 4900 ppm. Although histopathology was not conducted on both sexes at 4900 ppm. Thyroid changes were limited to minimal increased height of the follicular epithelium in males (6/23) at 4900 ppm. Although histopathology was not conducted on female rats received Ethofenprox (MTI-500) technical (96.3% purity) by average at 0 (1% methylcellulose), 12.5, 25, and 5000 mg/kg/day on gestation days 6 through 17, 21-24 per group were sacrificed on gestation day 20 for teratogenicity evaluation. Remaining females per group were all allowed to give birth and rear the offspring day 21. An F1 generation was selected from those pups to assess the reproductive effects of their previous exposure to ethofenprox. The untreated reproductive phase continued through weaning of the F2 generation. Teratogenicity phase results: Increased salivation was noted for dams at 250 and 5000 mg/kg/day. Weibrown staining around the mouth and wetgellow stained fur around the anogenital region were increased at 5000 mg/kg/day. The incidence of fetal visceral malformations was slightly higher at 5000 mg/kg/day. One fetus from each of 3 females was unaffected. 1 fetuses with microphthalmia, another with internal hydrocephaly and absent innominate artery, and a third with right microphthalmia and left anophthalmia were noted. The incidence was not statistically significant on a litter basis. Maternal NOEL = 250 mg/kg/day (increased wetbrown staining around the mouth and wetgellow stained fur around the anogenital region at 5000 mg/kg/day). Developmental NOEL = 5000 mg/kg/day. Reproductive

Teratology, Rabbit

51626-017 186451, "Rabbit Developmental Toxicity Study with Etofenprox", (James L. Ivett, Covance Laboratories, Inc., Vienna, VA., Covance study No. 6648-144, 17 January 2001). Twenty mated Hra:(NZW)SPF female rabbits per group were dosed by oral gavage with Etofenprox technical (96.68% purity) at 0 (1% aqueous methylcellulose), 30, 100, and 300 mg/kg/day on gestation days 6 through 28. There were no signs of maternal toxicity in any of the dose groups including clinical signs, bodyweights, bodyweight change, and food consumption. No external findings in any of the fetuses were recorded. No changes in fetal viability or fetal weight were indicated. Maternal NOEL = 300 mg/kg/day. Developmental NOEL was not determined due to incomplete fetal evaluation. **Unacceptable, not upgradeable** (incomplete fetal visceral exam, no skeletal exam). (Green and Gee, 4/4/03).

51626-017 186450, "Dose Range-Finding Developmental Toxicity Study in Rabbits with Etofenprox", (James L. Ivett, Covance Laboratories, Inc., Vienna, VA, Covance Study No. 6648-143, 13 September 2000). Five mated Hra:(NZW)SPF female rabbits per group received etofenprox (96.68% purity) by oral gavage at 0 (1% methylcellulose), 50, 125, 250, and 500 mg/kg/day on gestation days 6 through 28. At 500 mg/kg/day, the incidence of dams with thin appearance and few or no feces was increased. Maternal bodyweight and food consumption were reduced and the number of abortions increased (3/5). Fetal viability and weight were also reduced at 500 mg/kg/day. Maternal and Developmental NOEL = 250 mg/kg/day. **Supplemental information.** (Green and Gee, 4/4/03).

**** 0023; 205046;** "Rabbit Developmental Toxicity Study with Etofenprox"; (B.R. Fisher; Covance Laboratories, Inc., Vienna, VA; Study ID. 6648-146; 9/13/00); Twenty-two mated Hra:(NZW)SPF rabbits/group were dosed orally by gavage with 0 (aqueous 1% methylcellulose), 30, 100 or 300 mg/kg/day of etofenprox technical (lot no. 21088, purity: 96.68%) from gestation day 6 through 28. One doe in the 300 mg/kg group died on study gestation day 26 while aborting. Another doe in the 100 mg/kg group died on gestation day 26. No signs of distress were noted prior to its death. One 300 mg/kg doe was euthanized in moribund condition on gestation day 16. Three does in the 300 mg/kg group and one in the 30 mg/kg group suffered abortions. The mean body weight gain for the 300 mg/kg females was less than that of the control ($p<0.01$). The mean food consumption over the dosing period was reduced as well ($p<0.01$). The mean body weights of the 300 mg/kg fetuses was less than that of the controls ($p<0.01$). Although there was an increased incidence of unossified 5th sternabrae for the 30 and 100 mg/kg fetuses ($p<0.05$), lack of or diminished ossification was not evident for other related skeletal structures. **Possible adverse effect:** incidence of abortions; **Maternal NOEL:** 100 mg/kg/day (based upon lower mean body weight, food consumption and increased incidence of abortion for the 300 mg/kg females); **Developmental NOEL:** 100 mg/kg/day (based upon lower mean body weights for the 300 mg/kg fetuses); **Study acceptable.** (Moore, 7/8/03)

Gene Mutation

****51626-019 186454,** "Reverse Mutation in *Salmonella typhimurium*", (C.N. Edwards and R. Forster; Life Science Research, Roma Toxicology Centre, Rome, Italy; LSR-RTC Report No. 162001-M-06185, 22 August 1985). *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 were exposed (triplicate plates, 2 trials) to ethofenprox (MTI-500) (96.3% purity), in the presence and absence of S9 activation, at 0 (DMSO), 200, 400, 800, 1600, and 3200 μ g/plate for 72 hours. A precipitate formed at 3200 μ g/plate. Positive controls were functional. No increase in revertant colonies. **Acceptable.** (Green and Gee, 3/10/03).

****51626-019 186452,** "Gene Mutation in Chinese Hamster V79 Cells", (A. H. Seeberg and R. Forster, Life Science Research, Roma Toxicology Centre, Rome, Italy, LSR-RTC Report No. 162002-M-06985, 22 August 1985). Chinese hamster V79 cells were exposed in triplicate (2 trials) to Ethofenprox (MTI-500) (96.3% purity) in the presence and absence of rat liver S9 activation at 0 (1% dimethylsulfoxide), 9.75, 19.5, 39.0, 78.0, and 156.0 μ g/ml (limit of solubility) for three hours. No increase in mutation frequency for 6-thioguanine resistance. **Acceptable.** (Green and Gee, 3/10/03).

**51626-019 186459, "Unscheduled DNA Synthesis in Human Cells, Cell Line: HeLa S3". (A.H. Seebberg and R. Forster, Life Science Research, Rome, Italy, LSR-RTC Report No. 162003- M-05785, 30 July 1985). Human HeLa S3 cells were exposed to ethofenate (MTI-500) (96.3%) in triplicate monolayer cultures at 0 (DMSO), 2.44, 4.88, 9.75, 19.5, and 39.0 µg/ml in the presence

**51626-019 186458, "MTI-500-a-CO: Assessment of its Ability to Cause Lethal DNA Damage in Strains of *Escherichia Coli*", (J. Bootman and K. May, Life Science Research Limited, Eye, Suffolk, England, LSR Report No. 85/MTO022/504, 2 October 1985). Duplicate suspensions (2-5 x 10⁶ cells/ml) of *Escherichia coli* strains WP2, WP67, and CM871 were exposed in the presence of rat liver S9 activation to MTI-500-a-CO (99.6%) at 0 (DMSO), 0 (untreated), 320, 1000, 3200, and 10000 µg/ml for 2 and 18 hours. Bacteria were diluted and plated after dilution and the number of colonies per plate scored after 1 day at 37°C. Cell lethality was not increased in repeat experiments (WP67 and CM871). Positive controls (2-aminoanthracene and mitomycin) were efficient strains (WP67 and CM871). Positive controls were exposed to ethofenate (MTI-500) (96.3%) in functional. Acceptable. (Green and Gee, 3/10/03).

**51626-019 186458, "MTI-500-a-CO: Assessment of its Ability to Cause Lethal DNA Damage in Strains of *Escherichia Coli*", (J. Bootman and K. May, Life Science Research Limited, Eye, Suffolk, England, LSR Report No. 85/MTO021/711, 22 November 1985). Cultured Human Peripheral Lymphocytes, (J. Bootman et al., Life Science Research Limited, Eye, Suffolk, England, LSR Report No. 85/MTO017/430, 17 July 1985). Cultures of male human blood lymphocytes in whole blood were exposed to MTI-500-a-CO (99.6%) in triplicate at 0 (DMSO), 0 (untreated medium), 2.5, 5.0, 10.0, and 20.0 µg/ml in the absence of S9 activation and retreated (without activation) for a further 22 hours. One hundred metaphases were scored per culture. Mitotic indices were used for evidence of toxicity. No increase in structural chromosomal aberrations. Positive controls were functional. Acceptable. (Green and Gee, 3/10/03).

**51626-019 186457, "In Vitro Assessment of the Clastogenic Activity of MTI-500-a-CO in Cultured Human Peripheral Lymphocytes", (J. Bootman et al., Life Science Research Limited, Eye, Suffolk, England, LSR Report No. 85/MTO021/711, 22 November 1985). Cultures of male human blood lymphocytes in peripheral lymphocytes, (J. Bootman et al., Life Science Research Limited, Eye, Suffolk, England, LSR Report No. 85/MTO017/430, 17 July 1985). Triplicate cultures of male human blood lymphocytes were exposed to ethofenate (MTI-500) (96.3%) at 0 (DMSO), 6.25, 12.5, 25.0, and 50.0 µg/ml in the absence of S9 activation for 2 and 24 hours respectively (activated cultures were washed after 2 hours, then retreated (without activation) for a further 22 hours). Triplicate cultures per concentration with 100 metaphases scored per culture. Mitotic indices were recorded. Positive controls were functional. No increase in structural chromosomal aberrations. Acceptable. (Green and Gee, 3/10/03).

**51626-019 186456, "In Vitro Assessment of the Clastogenic Activity of MTI-500, Ethofenprox, Marrow Erythrocytes in the Micronucleus Test", (J. Bootman, et al., Life Science Research, Eye, Suffolk, England, LSR Report No. 85/MTO016/406, 3 July 1985). 15 (control and high dose) or 5 CD-1 mice per sex per group received a single oral gavage dose of ethofenprox (MTI-500) at 0 (0.5% methylcellulose), 80, 400, and 2000 mg/kg. Further lots of 5 animals per sex sacrificed 24 hours after treatment for bone marrow evaluation. Further lots of 5 animals per sex from the control and high dose groups were sacrificed 48 and 72 hours post-dosing. Approximately 2000 erythrocytes were scored per animal. The positive control, chlorambucil, was functionally 2000 control and high dose groups were scored groups were scored after 48 and 72 hours marrow evaluation. Further lots of 5 animals per sex from the control and high dose groups were scored per animal. The positive control, chlorambucil, was functionally 2000 increase in micronucleated polychromatic erythrocytes. Acceptable. (Green and Gee, 3/10/03).

**51626-019 186455, "MTI-500, Ethofenprox: Assessment of Clastogenic Action on Bone and *Salmonella typhimurium* strains TA 97A, TA 98, TA 100, TA 102, TA 1535, and TA 1537 S. Typhimurium strains TA 97A, TA 98, TA 100, TA 102, TA 1535, and TA 1537 Scienze Research Limited, Eye, Suffolk, England, LSR Report No. 85/MTO020/433, 19 July 1985). *Salmonella typhimurium* strains TA 97A, TA 98, TA 100, TA 102, TA 1535, and TA 1537 and *Escherichia coli* strain WP2 UVR were exposed, in triplicate, in the presence and absence of rat liver S9 activation, to MTI-500-a-CO (99.6% purity) at 0 (DMSO), 50, 158, 500, 1582, and 5000 µg/ml in the presence of mutation frequency. Positive controls were functional.

**51626-019 186453, "MTI-500-a-CO: Assessment of its Mutagenic Potential in Amino-Acid Auxotrophs of *Salmonella typhimurium* and *Escherichia coli*", (J. Bootman and K. May, Life Science Research Limited, Eye, Suffolk, England, LSR Report No. 85/MTO020/433, 19 July 1985). *Salmonella typhimurium* strains TA 97A, TA 98, TA 100, TA 102, TA 1535, and TA 1537 and *Escherichia coli* strain WP2 UVR were exposed, in triplicate, in the presence and absence of rat liver S9 activation, to MTI-500-a-CO (99.6% purity) at 0 (DMSO), 50, 158, 500, 1582, and 5000 µg/ml in the presence of mutation frequency. Positive controls were functional.

Chromosome Effects

Acceptable. (Green and Gee, 4/8/03).

Acceptable. (Green and Gee, 4/8/03).

of rat liver S9 mix and at 0 (DMSO), 9.75, 19.5, 39.0, 78.0, and 156 µg/ml without S9 for 3 hours in the presence of [³H] thymidine in two trials. The highest concentration was based on toxicity and solubility. Replicative DNA synthesis was suppressed in arginine free medium and by hydroxyurea during exposure. DNA was extracted from cell pellets by trichloroacetic acid precipitation followed by hydrolysis in 0.3 M KOH with heating. Label incorporation was determined by LSC and DNA concentration by a colorimetric assay. Results were expressed as DPM/µg DNA. Positive controls (4-NQO and B(a)P) were functional. No increase in unscheduled DNA synthesis. **Acceptable.** (Green and Gee, 4/9/03).

STUDIES ON METABOLITES

005; 186415; "MTI-500 α-Co: Acute Toxicity Study in the Rat" (Cummins, H.A. and Gardner, J.R., Life Science Research Limited, Eye, Suffolk, England, Laboratory Project ID 85/MT0018/474, 8/2/85). MTI-500 α-Co (Batch OFU-1021, purity = 99.6%), suspended in maize oil, was administered as a single gavage dose to 5 CD rats (remote Sprague-Dawley origin) per sex at a dose level of 5000 mg/kg. No mortalities occurred. Decreased motor activity was observed in all animals 2 hours after dosing clearing in all animals 4 hours after dosing. Necropsy revealed dark submandibular salivary glands in 2 males and large cervical lymph nodes in 1 male. LD₅₀ (M/F) > 5000 mg/kg. NOEL not determined. **Supplemental study** (the test material used in the study was not the active ingredient in review) (Corlett, 11/6/02)

005; 186416; "Ethofenprox (MTI-500) Acute Limit Test of Toxicity to Dogs Following a Single Oral Administration" (Harling, R.J. et al., Department of Dog Toxicology, Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, England, Laboratory Project ID MTC 101/851185, 10/24/85). Ethofenprox (MTI-500) (Batch ST103, purity = 96.3%) was inserted into gelatine capsules and 1 pure-bred beagle dog per sex was dosed once with 5000 mg/kg. No mortalities occurred. Semi-soft green feces approximately 2 hours after dosing and semi-soft feces of normal color on Days 2 and 4 were observed in the male; no clinical signs were observed in the female. Small weight loss was observed in the female for 3 days following dosing and at the end of the 14 day observation period. Necropsy revealed no treatment-related abnormalities. Bone marrow smears taken from each animal prior to terminal sacrifice were found to be normal in cellularity, morphology, and cell distribution. LD₅₀ (M/F) > 5000 mg/kg. NOEL not determined. **Supplemental study** (only 1 animal per sex per dose group used) (Corlett, 11/6/02)

CONCLUSIONS: Do data support registration?

Toxicity data were submitted to support a Section 3 registration request for Etofenprox Technical for manufacturing use only.

The acute oral and dermal toxicity and primary dermal and ocular irritation studies are acceptable. In contrast, the inhalation toxicity study is unacceptable but possibly upgradeable with submission of additional data to eliminate the deficiencies indicated in the one-liner above. MTI-500 is not a potential dermal sensitizer as indicated by the dermal sensitization study. Acceptable acute studies were submitted for a formulated product, Zoecon F254-87-1 Aerosol.

Subchronic oral feeding studies with rodents and 28-day repeated dose dermal toxicity studies are acceptable. However, the 90-day inhalation study in rats is unacceptable but may be upgradeable with submission of data and calculations used to determine the reported mean analytical concentrations of the test material.

Animal metabolism studies in dogs and rats were submitted. Collectively, the data fulfills the current requirements for an acceptable metabolism study.

RECOMMENDATIONS: What type of registration action is being considered? In the case of ongoing registration, register or do not register? What other specific studies or data are requested?

Acceptable studies were submitted to satisfy the current data requirements for gene mutation, chromosomal effects and DNA effects.

The rat and rabbit developmental and reproduction studies are acceptable.

Chronic feeding studies in rodents (rats and mice) are acceptable. However, the chronic toxicity study in dogs is not acceptable but may be upgradeable with submission of additional data to justify the dose levels selected.

Submitted as a Section 3 registration request for manufacturing use only.

The data reviewed are inadequate for a complete toxicological evaluation. The acute inhalation toxicity study is unacceptable but possibly upgradeable with submission of additional data to eliminate the deficiencies indicated in the one-liners. The 90-day inhalation study in rats is unacceptable but may be upgradeable with submission of data and calculations used to determine the reported mean analytical concentrations of the test material. Another unacceptable study is the chronic oral toxicity study in dogs (inadequate dose level selection). This study may be upgradeable with submission of dose level justification.

Registration is not recommended at this time.

Senior Toxicologist
Joyce Gee, Ph.D.

Senior Toxicologist
Peter Leung, Ph.D.

Staff Toxicologist
Thomas Moore, Ph.D.

Date
8/6/03

Date
8/6/03

Date
8-5-03

TO: Steve Rhodes, Senior Pesticide Use Specialist
Pesticide Registration Branch

FROM: Medical Toxicology Branch

Original Date: 4/21/03
Revised: 7/28/03
Revised: 9/16/03

PRODUCT REGISTRATION RECOMMENDATION SHEET

Formulated Product Name: Etofenprox Technical

Chemical Code #: 2292

ID #: 193825N

EPA Reg. #: 33657-6

SB 950 #: NA

Document #: 51626-002, -005 to -013, and -016 to -020, -023, -0024

Company Name: Mitsui Chemicals, Inc.

RECOMMENDATION:

Submitted as a Section 3 registration request for manufacturing use only.

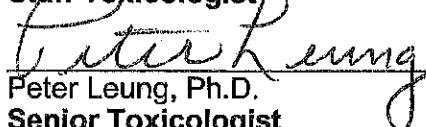
The data reviewed are inadequate for a complete toxicological evaluation. The acute inhalation toxicity study is unacceptable but possibly upgradeable with submission of additional data to eliminate the deficiencies indicated in the one-liners. The 90-day inhalation study in rats is unacceptable but may be upgradeable with submission of data and calculations used to determine the reported mean analytical concentrations of the test material.

Registration is not recommended at this time.


Thomas Moore, Ph.D.
Staff Toxicologist

7-17-03

Date


Peter Leung, Ph.D.
Senior Toxicologist

9/17/03

Date


Joyce Gee, Ph.D.
Senior Toxicologist

9/18/03

Date

Acute Dermal Toxicity

002; 068280; "Report on Acute Toxicity Study of MTI-500 (Ethofenprox) in Rats" (Hashimoto, K., Hatano Research Institute, FDSC, Hatano, Kanagawa, Japan, Project No. A-82-27~34, 10/21/82). 812. MTI-500 (Lot # ST-102, purity = 96%), warmed in a water bath and applied to the clipped skin of 10 Sprague-Dawley rats per sex per dose at a dose level of 2.144 g/kg for 24 hours. No mortalities occurred. Crouching and a reduction in spontaneous movement were observed in all animals 1 or 2 hours after application. Necropsy revealed no treatment-related abnormalities. Reported LD₅₀ (M/F) > 2.144 g/kg. Toxicity Category not determined.

Unacceptable but possibly upgradable with submission of information detailing how the test article was held in contact with the skin during the exposure period. (Corlett, 11/4/02)

002; 068281; "Report on Acute Toxicity Study of MTI-500 (Ethofenprox) in Mice" (Hashimoto, K., Hatano Research Institute, FDSC, Hatano, Kanagawa, Japan, Project No. A-82-35~42, 10/21/82). 812. MTI-500 (Lot # ST-102, purity = 96%), warmed in a water bath and applied to the clipped skin of 10 ICR mice per sex per dose at dose levels of 1.072 and 2.144 g/kg for 24 hours. No mortalities occurred. No clinical signs were observed. Necropsy revealed no treatment-related abnormalities. Reported LD₅₀ (M/F) > 2.144 g/kg. Toxicity Category not determined. **Unacceptable but possibly upgradable** with submission of information detailing how the test article was held in contact with the skin during the exposure period. (Corlett, 11/4/02)

51626-0023; 205045; "Acute Dermal Toxicity Study of Etofenprox in Rats"; (S. Oda; Bozo Research Center, Inc., Gotemba Laboratory, Setagaya-ku, Tokyo 156-0042, Japan; Project ID. B-5040; 2/5/03); The skin of five Sprague-Dawley (Crj:CD(SD)IGS) rats/sex was treated with 0 or 2000 mg/kg of etofenprox technical (lot. no. 20024, purity: 99.0%) for 24 hours under an occlusive wrap. No deaths resulted from the treatment. No treatment-related clinical signs were evident. In the necropsy examination, no treatment-related lesions were noted. LD₅₀ (M/F) > 2000 mg/kg; Toxicity Category III; **Study acceptable**. (Moore, 7/25/03)

Acute Inhalation Toxicity

002; 068282; "MTI-500 Acute Inhalation Toxicity in Rats 4 Hour Exposure" (Jackson, G.C. et al., Huntingdon Research Centre, Huntingdon, Cambridgeshire, England, HRC Report No. MTC 60/821079, 4/2/86 (re-issue)). 813. MTI-500 (Lot No. ST-101, purity = 96%) was blended with acetone, aerosolized, and administered in a whole body manner to 5 COBS® rats per sex at a dose level (reported mean analytical concentration) of 5.9 mg/l (95% of the test material < 5.5 µm aerodynamic diameter) for 4 hours. No mortalities occurred. Treatment-related clinical signs included closing or partial closing of eyes and dyspnea during exposure, and oily fur, lethargy, hair loss (females only), and hyperactivity during the 14 day observation period. Necropsy revealed no treatment-related abnormalities except for a black area on the liver of 1 male. Reported LC₅₀ (M/F) > 5.9 mg/l. Toxicity Category not determined. **Unacceptable but possibly upgradable** with a clarification on the amount of acetone blended with the test material and the submission of the data and calculations used to determine the mean analytical concentration of the test material (Corlett, 10/10/02)

Primary Eye Irritation

002; 068285; "MTI-500 Primary Ophthalmic Stimulation Test in Rabbits" (Kashima, M., Haruna Laboratory, Nippon Experimental Medical Research Institute, Ltd., Agatsuma-gun, Gunma Prefecture, Japan, Project No. Nemri-H-85-55, 10/24/85). 814. 0.1 ml of MTI-500 (Lot No. ST-103, purity = 96.3%) was placed into the conjunctival sac of 1 eye of each of 6 Japanese White rabbits. No corneal opacity or iritis was observed in any treated eye. Grade 1 conjunctival irritation was observed in 5 of 6 treated eyes 24 hours after treatment with all signs of conjunctival irritation clearing in all treated eyes 72 hours after treatment. Toxicity Category IV. **Acceptable**. (Corlett, 10/25/02)

002; 068283; "MTI-500 Skin Sensitization Test in Guinea Pigs" (Kobayashi, K., Ozum, Japan, no study or project number provided, 10/31/85). A modification of the Magnusson and Kligman maximization assay was used to assess the potential of MTI-500 (Lot No. ST-103, and Kligman, no study or project number provided, 10/31/85). A modified version of the Magnusson and Kligman maximization assay was used to elicit delayed contact hypersensitivity in the guinea pig. 20 English Harely guinea pigs were treated with the test material during the induction phase (intradermal injections followed 7 days later by a topical application) and during the challenge (topical application 14 days following the topical induction dose). A concurrent negative control group consisting of 20 animals was also included in the study. The control animals were treated identically to the test animals except that during induction the test material was replaced with vehicle. Observations 24 hours after the challenge dose did not indicate any skin-sensitization reaction.

SUPPLEMENTAL

002; 068284; "MTI-500 Primary Skin Stimulation Test in Rabbits" (Kashima, M., Haruna Laboratory, Nippon Experimental Medical Research Institute, Ltd., Agatsuma-gun, Gunma Prefecture, Japan, Project No. Nemii-H-85-5, 8/23/85). 815, 5 ml (sic) of MTI-500 (Lot No. ST-103, purity = 96.3%) was applied to the clipped and shaved skin of the back of each of 6 Japanese White rabbits using a semi-occlusive wrap. No edema was observed at any test site. Grade 1 erythema was first observed in 1 animal 48 hours after patch removal, persisting through 7 days after patch removal and clearing 8 days after patch removal. Toxicity Category IV. Acceptable. (Corlett, 10/24/02)

002; 068280; "Report on Acute Toxicity Study of MTI-500 (Ethofenprox) in Rats" (Hashimoto, K., Hatano Research Institute, FDSC, Hatano, Kanagawa, Japan, Project No. A-82-27~34, 10/21/82). MTI-500 (Lot # ST-101, purity = 96%), warmed in a water bath and administered intraperitoneally to 10 Sprague-Dawley rats per sex per dose at dose levels of 21.44 and 42.88 g/kg and observed for 14 days. No mortalities occurred. Piloerection and crouching with hollowed belly were observed immediately after dosing at both 21.44 and 42.88 g/kg. Diarrhea or soft stools were observed in all animals the day after test article administration. Necropsy revealed whitish yellow granules adhering to various organs in the abdomen including the fat tissue of the abdominal wall, omentum and mesenterium and around the testes in all animals; hemorrhagic points scattered in the lungs, congestion of the liver, and minor granuloma on the serous membrane of the liver and spleen and on the parietal peritoneum were also observed. LD₅₀ (M/F) > 42.88 g/kg. NOEL not determined. **Supplemental study** (not a guideline study) (Corlett, 11/4/02)

002; 068281; "Report on Acute Toxicity Study of MTI-500 (Ethofenprox) in Mice" (Hashimoto, K., Hatano Research Institute, FDSC, Hatano, Kanagawa, Japan, Project No. A-82-35~42, 10/21/82). MTI-500 (Lot # ST-102, purity = 96%), warmed in a water bath and administered intraperitoneally to 10 ICR mice per sex per dose at dose levels of 6.70, 13.40, 26.80, and 53.60 g/kg and observed for 21 days. Mortalities occurred as follows- males: 2/10, 3/10, 4/10, 3/10, respectively; females: 0/10, 1/10, 7/10, 7/10, respectively. 15 minutes after dosing, reduced appetite and reduced spontaneous movements were observed at all dose levels. 1 day after dosing, piloerection, facial edema, abdominal swelling, and soft stools were observed. Histopathological examination revealed the formation of minor granuloma in the serous membranes of liver, spleen, pancreas, and digestive tract. LD₅₀ (M/F) not determined. NOEL not determined. **Supplemental study** (not a guideline study) (Corlett, 11/4/02)

ACUTE STUDIES - Zoecon F254-87-1 Aerosol

	Toxicity Category
Acute Oral Toxicity LD50	IV
Acute Dermal Toxicity LD50	III
Acute Inhalation Toxicity LC50	IV
Primary Eye Irritation	IV
Primary Dermal Irritation	III
Dermal Sensitization	Not a sensitizer

Acute Oral Toxicity

002; 068288; "Acute Oral Toxicity Study in Rats Administered Test Article Zoecon F254-87-1 Aerosol, Lot No. L255-140-1" (Davis, T.K., UBTL, Inc., Salt Lake City, UT, Study #63296, 5/8/87). 811. Zoecon F254-87-1 Aerosol (Lot No. L255-140-1, 1.3% etofenprox, 0.38% (S)-hydropropene) was administered as a single gavage dose to 5 Sprague Dawley rats per sex per dose at a dose level of 5.1 g/kg. No mortalities occurred. Nasal discharge was observed in 2 animals on the day of dosing clearing in both animals on the next day. Necropsy revealed kidneys exhibiting light red to dark red mottled appearance in 1/5 males and in 2/5 females and each kidney exhibiting 2-12 infarcts in 3/5 males and 3/5 females. LD₅₀ (M/F) > 5.1 g/kg. Toxicity Category IV.
Acceptable. (Corlett, 10/30/02)

Acute Dermal Toxicity

002; 068287; "Acute Dermal Toxicity Study in Rabbits Administered Test Article Zoecon F254-87-1 Aerosol, Lot No. L255-140-1" (Davis, T.K., UBTL, Inc., Salt Lake City, UT, Study #63297, 5/8/87). 812. Zoecon F254-87-1 Aerosol (Lot No. L255-140-1, 1.3% etofenprox, 0.38% (S)-hydropropene) was applied to the clipped skin of 5 New Zealand White rabbits per sex per dose at a dose level of 2.1 g/kg for 24 hours. No mortalities occurred. No treatment-related clinical signs were observed. Erythema was observed in all animals after patch removal; edema and eschar were also observed in some animals. Necropsy revealed dry skin at the exposure site in 1 male

Acute Inhalation Toxicity

002; 068286, "The Acute Toxicity of Inhaled Zoecon F254-87-1 Aerosol (Lot No. L255-140-1 and L255-149-1) in the Albino Rat (Safety Test)" (Vau, A. et al., Bio-Research Laboratories Ltd., Senneville, Quebec, Canada, Project No. 82969, 6/8/87). 813, F254-87-1 Aerosol (Lot No. L255-140-1 and L255-149-1, 1.3% etofenprox, 0.4% (S)-hydroperene) was aerosolized and administered in a whole body manner to 5 Crl:CD[®](SD)BR rats per sex at a dose level (mean gravimetric concentration) of 4.32 mg/l (mean mass median particle diameter 10 cm of Zoecon F254-87-1 Aerosol, Lot No. L255-140-1, 1.3% etofenprox, 0.4% (S)-hydroperene) for 4 hours. No mortalities occurred. Treatment-related clinical signs included partial closing of eyes, inactivity, and slightly wet fur during exposure, and red muzzle staining, pale eye color, drowsiness, and rough and wet fur after exposure; all signs cleared the next day. Necropsy revealed no treatment-related abnormalities. LC₅₀ (M/F) > 4.32 mg/l. Toxicity Category IV. Acceptable.

Primary Eye Irritation

002; 068289, "Primary Eye Irritation Study in Rabbits Administered Test Article Zoecon F254-87-1 Aerosol, Lot No. L255-140-1" (Davis, T.K., UBTI, Inc., Salt Lake City, UT, Study #63298, 5/8/87). 814, A single, second burst from a distance of approximately 10 cm of Zoecon F254-87-1 Aerosol (Lot No. L255-140-1, 1.3% etofenprox, 0.4% (S)-hydroperene) was administered to 9 New Zealand white rabbits. 1 eye of each of 9 New Zealand white rabbits, 3 of the treated eyes were washed and 6 were not washed. No corneal opacity or irritation was observed in any unwashed treated eye. Grade 1 conjunctival irritation was observed in 3 of 6 unwashed treated eyes 1 hour after treatment with all etofenprox, 0.4% (S)-hydroperene) was applied to each of 2 sites on the clipped skin of each of 6 New Zealand rabbits for 4 hours. Grade 2 erythema was observed in all animals 24 and 72 hours after patch removal, decreasing to grade 2 in 2 animals and grade 1 in 4 animals 7 days after patch removal, and decreasing to grade 1 in 3 animals 14 days after patch removal. Grade 1 edema was observed in 3 animals 24 hours after patch removal and in 1 animal 72 hours after patch removal with all signs of edema clearing in all animals 7 days after patch removal. Toxicity Category III. Acceptable. (Corlett, 10/31/02)

Dermal Sensitization

002; 068290, "Dermal Sensitization Study in Albino Guinea Pigs Administered Test Article Zoecon F254-87-1 Aerosol, Lot No. L255-140-1" (Davis, T.K., UBTI, Inc., Salt Lake City, UT, Study #63300, 5/8/87). 816, A modified version of the Buehler method was used to assess the skin sensitization potential of Zoecon F254-87-1 Aerosol (Lot No. L255-140-1, 1.3% etofenprox, 0.38% (S)-hydroperene). 10 Hartley albino guinea pigs were treated with the test material. Each animal was then challenged with the same induction dose at a naive site on each animal, 2 weeks following the third induction dose, for 6 hours. The test material produced a positive result in 20% of the treated animals 48 hours after challenge application. Positive controls functional.

The results of this study indicate that the test material is a potential contact sensitizer when using this modified version of the method of Buehler. Acceptable. (Corlett, 11/4/02)

Acute Inhalation Toxicity

III. Acceptable. (Corlett, 10/30/02)
and 4 females; no internal abnormalities were observed. LD₅₀ (M/F) > 2.1 g/kg. Toxicity Category III. Acceptable. (Corlett, 10/30/02)

SUBCHRONIC STUDIES

(Oral)

007; 186424; "Assessment of the Toxicity of MTI-500 in Rats by Dietary Administration for 13 Weeks" (Green, O.P. et al., Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, England, Laboratory Project ID MTC 56/821067/2, 4/2/86). 821. MTI-500 (Batch No. ST-101, purity = 96%) was admixed to the diet and fed to 20 CD rats per sex per dose at dose levels of 0 (diet and corn oil only), 50, 300, 1800, or 10800 ppm (0, 3.3, 20, 120, 734 mg/kg/day, respectively, for males and 0, 3.8, 23, 142, 820 mg/kg/day, respectively, for females) for 13 weeks. No treatment-related mortalities occurred. No treatment-related clinical signs were observed. A treatment-related decrease in mean thyroxine (T_4) levels in males at 1800 and 10800 ppm was observed. Treatment-related increases in mean adjusted liver weight in males at 10800 ppm and in females at 1800 and 10800 ppm and mean adjusted thyroid weight in males at 1800 and 10800 ppm were observed. Microscopic examination revealed an increased incidence of microfollicles in the thyroid in males at 1800 and 10800 ppm and in females at 10800 ppm and enlargement of the centrilobular hepatocytes in females at 10800 ppm. **No adverse effects.** NOEL (M) = 20 mg/kg/day (300 ppm) based on an increased incidence of microfollicles in the thyroid, NOEL (F) = 23 mg/kg/day (300 ppm) based on increased liver weights and enlargement of the centrilobular hepatocytes. **Acceptable.** (Corlett, 11/22/02)

006; 186423; "Assessment of the Toxicity of MTI-500 to Mice by Dietary Administration for 13 Weeks" (Green, O.P. et al., Huntingdon Research Centre plc, Huntingdon, Cambridgeshire, England, Laboratory Project ID MTC 55/821112/2, 4/2/86). 821. MTI-500 (Batch No. ST-103, purity = 96%) was admixed to the diet and fed to 20 CD-1 mice per sex per dose at dose levels of 0 (diet and corn oil only), 50, 500, 3000, or 15000 ppm (0, 6.1, 60, 375, 1975 mg/kg/day, respectively, for males and 0, 6.9, 71, 390, 2192 mg/kg/day, respectively, for females) for 13 weeks. 2 males and 6 females at 15000 ppm died or were killed for humane reasons and these deaths are considered treatment-related. At 15000 ppm, treatment-related piloerection, hunched posture, emaciated and/or anemic appearance, body tremors, and respiratory distress in both sexes, and lethargy and unsteady gait in females were observed. Treatment-related decreased body weight gain and increased water consumption were observed in both sexes at 15000 ppm. Treatment-related increases in mean urea nitrogen and cholesterol levels and in mean relative liver and kidney weights were observed in both sexes at 15000 ppm. Macroscopic examination revealed kidneys that were pale, enlarged, and with cortical scarring in both sexes at 15000 ppm. Microscopic examination revealed kidneys with widespread tubular basophilia, extensive tubular dilatation, and dilatation of the renal pelvis, centrilobular hepatocyte enlargement, increased cellularity of splenic white pulp, and lymphoid hyperplasia in both sexes at 15000 ppm. **No adverse effects.** NOEL (M) = 375 mg/kg/day (3000 ppm), NOEL (F) = 390 mg/kg/day (3000 ppm) based on kidneys with widespread tubular basophilia and extensive tubular dilatation. **Acceptable.** (Corlett, 11/18/02)

(Dermal)

008; 186425; "A 28-Day Repeated Dose Dermal Toxicity Study in Rabbits with Technical MTI-500" (Killeen, J.C., Jr., Toxicology & Metabolism, Ricerca, LLC, Painesville, OH, Document No. 011077-1, 6/28/00). 870.32. Technical MTI-500 (Lot No. 21049, purity = 99.18%) was applied to the clipped dorsal skin of 10 New Zealand White rabbits per sex per dose at dose levels of 0 (tap water only), 400, 650, or 1000 mg/kg/day for 6 hours per day, for 28 consecutive days. In addition, 10 animals per sex at the control and high dose levels were used to assess recovery (recovery group animals were observed for an additional 2 weeks after the others were sacrificed). No mortalities occurred. No treatment-related systemic clinical signs were observed. Body weight and organ weight determinations along with hematology and serum chemistry revealed no treatment-related effects. Treatment-related erythema at the test site was observed at the 400, 650 and 1000 mg/kg/day dose levels in both sexes throughout the 28-day treatment period. Microscopic examination revealed treated skin where the epidermis exhibited treatment-related diffuse hyperplasia at 400, 650, and 1000 mg/kg/day in both sexes; treated recovery group animals did not significantly exhibit this effect. **No adverse effects.** NOEL (M/F, systemic) = 1000 mg/kg/day based on no treatment-related effects at the highest dose tested; NOEL (M/F,

**51626-020 186460, "The Metabolism of ^{14}C -Ethofenprox in Dogs", (D. R. Hawkins, et al., Department of Chemical Metabolism and Radiosynthesis, Huntington Research Centre, Huntington, Cambridgeshire, England, HRC Report No. HRC/MTC 69/84583, 11 October 1985). Two Beagle dogs per sex received a single oral gavage dose of ^{14}C -Ethofenprox at 30 mg/kg. Radiolactivity was excreted mainly in the feces. 86.7% of the dose was excreted in the feces during the first 24 hours. 89.5% (mean of 4 animals) was excreted during the five days after dosing. Excretion of radiocactivity in urine (including cage wash) accounted for a mean of 6.2% of the dose in 5 days of which 5.0% was eliminated within 24 hours after treatment. Unchanged ethofenprox accounted for 91.4% and 93.3% of the radiocactivity excreted from feces (0-24 hours post-dosing) of males and females respectively, equivalent to 48.5% and 59% of the dose respectively. The next most plentiful components in feces were 2 metabolites, one from O-de-ethylatoin of the ethoxypyhenyl moiety, and, the other, from aromatic ring-hydroxylation of the phenoxypybenzyl moiety of ethofenprox. They accounted for 6.1% (male) and 4.6% (female) of plasma concentrations peaked from 15 minutes to 3 hours after dosing at 4.43 to 7.16 $\mu\text{g}/\text{ml}$. Plasma concentrations of radiolabels were found in the liver (range 3.1 to 9.6 $\mu\text{g}/\text{g}$). Whole liver concentrations of radiocactivity were found in the kidneys and fat. Lowest concentrations were found in gall bladder, muscle, heart, lung, brain, and skin. Next highest concentrations were found in kidney, liver, and muscle. Highest concentrations were found in the gall bladder of 2 animals, contained very high radioactivity levels. Acceptable. (Green and Gee, 4/10/03).

METABOLISM STUDIES

009; 186426, "Ethofenprox (MTI-500) 90-Day Inhalation Study in Rats" (Coombs, D.W. et al., MTC 81/841257, 8/23/85). 824, Ethofenprox (MTI-500), Batch No. ST 103, purity = 96% was mixed with acetone (90% test article; 10% acetone, w/w), aerosolized, and administered in a whole-body manner to 15 Wistar rats per sex per dose at dose levels (reported mean analytical concentration) of 0 (air control), 0 (acetone only, at a concentration equal to the acetone of the test material < 5.5 μ m equivalent aerodynamic diameter) for 6 hours per day 6 days per week for 13 consecutive weeks. No mortalities were reported. Treatment-related scab formation at the back of the ears was observed in males at 1.01 mg/l and in females at 0.21 and 1.01 mg/l. Treatment-related increases in mean liver and thyroid weights in both sexes at 1.01 mg/l and mean adrenal weight in females at 0.21 and 1.01 mg/l were observed. Microscopic examination revealed minimal enlargement of centrilobular hepatocytes in both sexes at 1.01 mg/l, a minimally increased number of microfollicles and a minimally increased height of follicular epithelium in the thyroid in males at 1.01 mg/l, and a minimally increased cortical width of adrenals at 0.21 and 1.01 mg/l. No adverse effects, NOEL (M) = 0.21 mg/l based on increased adrenal weight increased number of microfollicles and minimally increased cortical width of adrenals in females at 0.21 and 1.01 mg/l. Together with a minimally increased corticosteroid secretion of centrilobular hepatocytes and increased weight of adrenals and minimally increased height of follicular epithelium in the thyroid; NOEL (F) = 0.042 mg/l based on enlarged adrenals and increased adrenal weight.

skin) < 400 mg/kg/day based on incidences of erythema and epidermis with diffuse hyperplasia. Acceptable. (Cohrte, 12/11/02)

Single (30 and 180 mg/kg) and multiple (30 mg/kg/day for 7 or 14 consecutive days) doses of ¹⁴C-ethofenprox were used for groups of 3, 5, or 25 CD rats per sex or 3 or 10 pregnant/lactating females per group to evaluate metabolic and pharmacokinetic parameters.

A single oral dose of ¹⁴C-ethofenprox at 30 mg/kg to 5 rats per sex was mainly eliminated in the feces. During the 5 days following dosing, means of 88.0% and 86.4% dose were excreted by males and females respectively by this route. Approximately equal amounts (35% to 40% of dose) were excreted by both sexes during the 0 to 24 hour and 24 to 48 hour periods. Excretion of radioactivity in the urine accounted for means of 10.8% (males) and 8.0% (females) over 5 days and most was excreted in the first 24 hours. Mean total retention of radioactivity in the bodies 5 days post-dosing was 3.4% (males) and 3.5% (females). The pattern of excretion of radioactivity after a single oral dose of ¹⁴C-ethofenprox to 5 per sex at 180 mg/kg was similar to that seen at 30 mg/kg. Tissue concentrations of radioactivity were measured at 120 hours after dosing. Highest mean tissue concentrations were found in fat of 30 mg/kg dosed animals (16.6 µg/g in males, 11.1 µg/g in females). Muscle concentrations were near the limit of accurate measurement (0.05 µg/g). Liver contained mean concentrations of 0.34 µg/g (males) and 0.33 µg/g (females). Mean kidney concentrations were 0.13 and 0.16 µg/g for males and females respectively. At 180 mg/kg, mean fat concentrations of radioactivity were 90.2 µg/g and 94.0 µg/g for males and females respectively 120 hours after dosing. Concentrations in other tissues were all below 2 µg/g. Unchanged ethofenprox accounted for 6.6% and 14.0% of dose for males and females respectively at 30 mg/kg, and, for 22.6% and 29.0% respectively at 180 mg/kg in extracts of rat feces collected during 72 hours. The metabolite desethylethofenprox was 19.5% (males) and 25.1% (females) at 30 mg/kg and 23.2% and 20.6% respectively at 180 mg/kg over the same time period. Another metabolite, 4'-hydroxyethofenprox, made up 13.2% and 13.8% at 30 mg/kg and 7.2% and 8.1% at 180 mg/kg of the extracts for males and females respectively.

After a single oral dose at 30 mg/kg to 5 per sex, peak plasma concentrations (approximately 5 µg/ml) occurred 2 to 7 hours later. Peak plasma concentrations (16 µg/ml to 17 µg/ml) were reached 5 hours post-dosing after a single dose of 180 mg/kg.

In a tissue distribution assay, 30 mg/kg/day of ¹⁴C-ethofenprox was administered to 25 rats per sex on seven consecutive days. 5 per sex were sacrificed for sampling at 4, 24, 48, 120, and 240 hours after the last dose. The highest concentrations of radioactivity in all tissues were found at 4 hours post-dosing. Fat contained the highest concentration (94.2 µg/g to 101 µg/g). Next highest concentrations (30.5 µg/g male, 22.3 µg/g female) were found in liver at 4 hours. The major component in fat and liver was unchanged ethofenprox.

10 pregnant female rats received 30 mg/kg/day of ¹⁴C-ethofenprox by oral intubation on gestation days 10 through 16. 2 dams were sacrificed for sampling at 4, 24, 48, 72, and 120 hours after the last dose. Adrenal glands, kidneys, heart, and liver showed radioactivity concentrations and patterns of elimination of radioactivity similar to non-pregnant animals. Of those, adrenal glands contained the highest concentrations, 61.5 µg/g at 4 hours, declining to 5.74 µg/g at 120 hours. Of the reproductive tissues, mammary contained the highest concentrations (87.4 µg/g at 4 hours declining to 32.4 µg/g at 120 hours after the last dose), similar to those in fat of non-pregnant animals. Radioactivity concentrations in placentae were lower than in any other maternal tissue. Concentrations declined from 4.6 µg/g to 4.8 µg/g at 4 hours to 0.17 µg/g at 120 hours. Maximum fetal concentrations were 1.6 µg/g to 1.7 µg/g at 4 hours.

Secretion of radioactivity into the milk of mother rats was evaluated by analysis of the stomach contents of suckling pups. Dams were treated with 30 mg/kg/day of ¹⁴C-ethofenprox by oral intubation from gestation day 18 through lactation day 9 (14 days total). Radioactivity concentration in pup stomach contents ranged from 41.3 µg/g to 88.3 µg/g after one hour of suckling compared to maternal plasma concentrations in the range of 1.9 µg/ml to 3.6 µg/ml. Chromatographic analysis indicated that 95% of the radioactivity ingested by the pups was associated with unchanged ethofenprox. **Acceptable.** (Green and Gee, 4/10/03).

MTC 71/85234, 25 October 1985). 6 (control and high dose) or 4 Beagle dogs per sex per Harling, et al., Huntingdon Research Centre, Ltd., Huntingdon, Cambridgeshire, England, Report # MTC 71/85234, 25 October 1985).

Dietary Administration for 52 Weeks Followed by a Recovery Period of 8 Weeks, (Robert J. ** 51626-010, -0024 186427, 205248, "Ethofenprox (MTI-500) Toxicity to Dogs by Repeated Chronic Toxicity, Dog

histopathology. Acceptable. (Green and Gee, 4/3/03).

Effects (thyroid tumors at 4900 ppm). 186439 is a photomicrography addendum for hepatotoxic liver changes, reduced bodyweight gain and food consumption). Possible adverse hepatotoxicities in main group animals at 700 and 4900 ppm. Chronic NOEL = 100 ppm (non-sacrifice (satellite) and at termination (main) in 4900 ppm animals and as increases in eosinophilic neoplastic changes were observed as increased centralobular hepatocyte enlargement at 26 weeks and a significant increase in females by pair wise comparison (0/50 versus 9/50). Non- thyroid adenomas plus carcinomas were increased at 4900 ppm with a positive significant trend in males and a sacrifice was noted. At termination, pale focus/focal in the lungs was increased in males and a significant increase in females by pair wise comparison (0/50 versus 9/50). Non- week sacrifice was noted. Enlarged thyroid was increased in 4900 ppm females at terminal sacrifice. females at 4900 ppm. Enlarged thyroid plus carcinomas were increased at 4900 ppm males at 26 weeks at week 26 and for 700 and 4900 ppm males at week 52. Increased liver enlargement for 4900 ppm males at scheduled and unscheduled sacrifice, and for females at 26 weeks at week 26 and for 700 and 4900 ppm males at week 52. Increased liver termination. Absolute (with statistical significance) and relative kidney weights were increased for 4900 ppm females receiving 4900 ppm during weeks 26 and 106 and for 700 ppm males at 4900 ppm females at week 26 and for 700 and 4900 ppm males at week 52. Increased liver weights were higher for 4900 ppm males at weeks 26 and 106 and for 700 ppm males at 4900 ppm females receiving 4900 ppm during weeks 5, 12, and 23. Statistically significant increases in absolute liver weight were recorded in both sexes at 4900 ppm for weeks 26, 52, and 110. and females receiving 4900 ppm during treatment period. Marginally lower water intake was noted for males 4900 ppm throughout the treatment period. Marginal increase in intake was received for 34% reductions in bodyweight gain for males and females respectively. 24% to 4.8, 25.5 and 34.3; and 186.7 and 249.1 mg/kg/day for males and females respectively. 24% to equivalents at 30, 100, 700, and 4900 ppm during the treatment period were 1.1 and 1.4, 3.7 and intervals and for interim sacrifice after 26 and 52 weeks of treatment. Group mean mg/kg/day through 110 weeks of treatment. Satellite animals were used for blood and urine sampling at satellite group animals respectively. Main group animals were used for tumorigenic evaluation 4900 ppm for 110 weeks. 50 and 20 animals per sex per group were designated main and 4900 ppm for MTI 500 technical (96.3%) in the diet at 0 (corn oil + basal diet), 30, 100, 700, and ethofenprox (MTI 500) rats per sex per group of Sprague-Dawley origin received 59/85581, 24 January 1986). 70 CD rats per sex per group of Sprague-Dawley origin received Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, England, Report # MTC Effects in Prolonged Dietary Administration to Rats (Final Report), (Owen P. Green, et al., Combined, Rat ** 51626-011, 012 186428, 186439, "Ethofenprox (MTI-500) Potential Tumorigenic and Toxic

SB950-MANDATED HEALTH EFFECTS STUDIES

Ge, 3/13/03).

5.07%, 6.10%, and 6.57% at 5, 59, and 184 $\mu\text{g}/\text{cm}^2$ after 96 hours. Acceptable. (Green and absorbed (found in blood, carcass, and excreta (urine, feces, cage wash and cage wipe) was 18.1% (mid dose), and 8.52% to 30.3% (high dose). The percentage of applied radioactivity The mean of applied radioactivity detected in or on skin was 4.59% to 13.5% (low dose), 7.07% to responding all time points, were 94.9%, 97.9%, and 122% of the total dose at 5, 59, and 184 $\mu\text{g}/\text{cm}^2$ including all time points, were 94.9%, 97.9%, and 122% of the total dose at 5, 59, and 184 $\mu\text{g}/\text{cm}^2$ (24- and 96-hour sacrifice animals) and the wash retained. Overall recoveries of radioactivity. 2% lysis just before sacrifice (1-and 10-hour sacrifice animals) or 10 hours after treatment Project Number CHW 6648-135, 4 January 1999). Shaved, washed, unbarred skin of the back and shoulders (12.5 cm²) of 16 CD BR SD male rats per group were sacrificed for analysis at 1, 10, 24, and 96 hours post-dosing. The skin at the application site was washed using ¹⁴C-Ethofenprox (MTI-500) at 5, 59, and 184 $\mu\text{g}/\text{cm}^2$. 4 animals per group were sacrificed for and "Definitive Phases", (Fred Thalacker, Covance Laboratories, Inc., Madison, WI, Laboratory ** 51626-020 186462, "Dermal Absorption of ¹⁴C-Ethofenprox in Male Rats (Preliminary and Preliminary Phases)", (Fred Thalacker, Covance Laboratories, Inc., Madison, WI, Laboratory

group received ethofenprox (MTI-500) (96.3% purity) in the diet at 0 (basal diet + corn oil), 100, 1000, and 10000 ppm for 52 weeks. In a recovery phase, 2 animals per sex from the control and high dose groups received untreated diet for 8 weeks following treatment. Mg/kg/day equivalents for males and females were 3.46 and 3.17; 33.37 and 32.19; and 351.73 and 339.32 at 100, 1000, and 10000 ppm respectively. Statistically significant decreases in total protein and cholesterol and increases in alkaline phosphatase were noted for 10000 ppm males and females from week 6 onwards. After 52 weeks of treatment, lung, liver, kidney, and pancreas weights (as % of bodyweight) were increased (statistical significance for liver) for both sexes at 10000 ppm relative to controls. One 1000 ppm female and 2 males and 1 female at 10000 ppm were noted with accentuation of the lobular markings of the liver at 52 week necropsy. Histopathology revealed 2/4 female dogs at 10000 ppm with minimal swelling of centrilobular liver cells at 52 weeks. The noted changes were generally diminished or absent after the 8 week recovery period. **No adverse effects.** **Chronic NOEL:** (M/F) 1000 ppm ((M): 33.37 mg/kg/day, (F) : 32.19 mg/kg/day) (based upon increased absolute and relative liver weights, increased serum alkaline phosphatase activity and swelling of the centrilobular liver cells in the 10000 ppm treatment group); Study previously unacceptable, possibly upgradeable with dose level justification; data submitted in vol. 51626-0024, rec. no. 205248 was sufficient to justify the dose. **Study acceptable.** (Green and Gee, 4/10/03, upgraded, Moore, 9/16/03).

Oncogenicity, Mouse

**51626-013, 016 186440, 186443, "Ethofenprox (MTI-500) Potential Tumorigenic and Toxic Effects in Prolonged Dietary Administration to Mice (Final Report)", (Owen P. Green, et al., Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, England, Report # MTC 58/85582, 6 January 1986). Seventy-six CD-1 mice (of Swiss origin) per sex per group received ethofenprox (MTI-500) technical (96.3%) in the diet at 0 (basal diet + corn oil), 30, 100, 700, and 4900 ppm for 108 weeks. Fifty-two per sex per group, designated main group animals, were treated through 108 weeks. The remaining 24 per sex per group satellite animals were used for blood and urine sampling at intervals through week 52 and for interim necropsies at 26 and 52 weeks. Mean mg/kg/day intake of ethofenprox for weeks 1 through 108 was 3.1 and 3.6, 10.4 and 11.7, 75.2 and 80.9, and 546.9 and 615.5 mg/kg/day for males and females at 30, 100, 700, and 4900 ppm respectively. For males at 4900 ppm, survival was reduced at study termination and bodyweight gain was decreased through week 52. Water consumption increased (statistically significant) for both sexes at 4900 ppm for weeks 5, 12, and 23 and urine volume was higher (statistically significant) for males at all treatment levels at week 52. Absolute (g) liver weights were higher (statistically significant) for males at 4900 ppm and relative liver weights (% bodyweight) were increased for both sexes. Also at necropsy, in both sexes, the incidence of pale kidneys was increased at 100, 700, and 4900 ppm and renal cortical scarring incidence was higher at 4900 ppm. Treatment related non-neoplastic changes were confined to the kidney. Increases in dilated/basophilic cortical tubules of varying severity were noted for both sexes at 100, 700, and 4900 ppm and for males at 30 ppm. This lesion was associated with focal loss of tubules at the higher dose levels. No carcinogenicity, no adverse effects. Chronic NOEL = 30 ppm (3.1 and 3.6 mg/kg/day in males and females respectively) (kidney changes). Record 186443 contains a photomicrography addendum for kidney changes. No evidence of oncogenicity. Acceptable. (Green and Gee, 4/2/03).

The study (record 186441) discussed the U.S. EPA classification of etofenprox as a Group C Oncogen on the basis of increased incidence (outside the historical control range for the performing laboratory) of thyroid follicular cell adenomas and adenomas/carcinomas combined in the rat. The authors requested a reclassification for etofenprox to Group D or E Oncogen based on the negative results of mice and dog studies previously conducted showing no thyroid oncogenicity. Also, on results of the *in vitro* studies (non-guideline protocols) in the appendix on the *in vitro* based effect of etofenprox on FRTL 5 (Fischer rat thyroid follicular cells). The broadening of the historical control pool that included more data for the strain from the rat supplier indicated more variability for thyroid effects than in the initial evaluation. Record 186442 appendix contains full copies of published literature listed in the references of 186441. Publications in

186442 were not given a review. The argument was being made for a non-genotoxic mechanism for thyroid tumor induction and the use of a MOE. (Green and Gee, 4/03/03).

Teratology, Rabbit

51626-017 186451, "Rabbit Developmental Toxicity Study with Etofenprox", (James L. Ivett, Covance Laboratories, Inc., Vienna, VA., Covance study No. 6648-144, 17 January 2001). 20 mated Hra:(NZW)SPF female rabbits per group were dosed by oral gavage with Etofenprox technical (96.68% purity) at 0 (1% aqueous methylcellulose), 30, 100, and 300 mg/kg/day on gestation days 6 through 28. There were no signs of maternal toxicity in any of the dose groups including clinical signs, bodyweights, bodyweight change, and food consumption. No external findings in any of the fetuses were recorded. No changes in fetal viability or fetal weight were indicated. Maternal NOEL = 300 mg/kg/day. Developmental NOEL was not determined due to incomplete fetal evaluation. **Unacceptable, not upgradeable** (incomplete fetal visceral exam, no skeletal exam). (Green and Gee, 4/4/03).

51626-017 186450, "Dose Range-Finding Developmental Toxicity Study in Rabbits with Etofenprox", (James L. Ivett, Covance Laboratories, Inc., Vienna, VA, Covance Study No. 6648-143, 13 September 2000). Five mated Hra:(NZW)SPF female rabbits per group received etofenprox (96.68% purity) by oral gavage at 0 (1% methylcellulose), 50, 125, 250, and 500 mg/kg/day on gestation days 6 through 28. At 500 mg/kg/day, the incidence of dams with thin appearance and few or no feces was increased. Maternal bodyweight and food consumption were reduced and the number of abortions increased (3/5). Fetal viability and weight were also reduced at 500 mg/kg/day. Maternal and Developmental NOEL = 250 mg/kg/day. **Supplemental information.** (Green and Gee, 4/4/03).

**** 0023; 205046;** "Rabbit Developmental Toxicity Study with Etofenprox"; (B.R. Fisher; Covance Laboratories, Inc., Vienna, VA; Study ID. 6648-146; 9/13/00); Twenty-two mated Hra:(NZW)SPF rabbits/group were dosed orally by gavage with 0 (aqueous 1% methylcellulose), 30, 100 or 300 mg/kg/day of etofenprox technical (lot no. 21088, purity: 96.68%) from gestation day 6 through 28. One doe in the 300 mg/kg group died on study gestation day 26 while aborting. Another doe in the 100 mg/kg group died on gestation day 26. No signs of distress were noted prior to its death. One 300 mg/kg doe was euthanized in moribund condition on gestation day 16. Three does in the 300 mg/kg group and one in the 30 mg/kg group suffered abortions. The mean body weight gain for the 300 mg/kg females was less than that of the control ($p<0.01$). The mean food consumption over the dosing period was reduced as well ($p<0.01$). The mean body weights of the 300 mg/kg fetuses was less than that of the controls ($p<0.01$). Although there was an increased incidence of unossified 5th sternabrae for the 30 and 100 mg/kg fetuses ($p<0.05$), lack of or diminished ossification was not evident for other related skeletal structures. **Possible adverse effect:** incidence of abortions; **Maternal NOEL:** 100 mg/kg/day (based upon lower mean body weight, food consumption and increased incidence of abortion for the 300 mg/kg females); **Developmental NOEL:** 100 mg/kg/day (based upon lower mean body weights for the 300 mg/kg fetuses); **Study acceptable.** (Moore, 7/8/03)

Gene Mutation

****51626-019 186454,** "Reverse Mutation in *Salmonella typhimurium*", (C.N. Edwards and R. Forster; Life Science Research, Roma Toxicology Centre, Rome, Italy; LSR-RTC Report No. 162001-M-06185, 22 August 1985). *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 were exposed (triplicate plates, 2 trials) to ethofenprox (MTI-500) (96.3% purity), in the presence and absence of S9 activation, at 0 (DMSO), 200, 400, 800, 1600, and 3200 μ g/plate for 72 hours. A precipitate formed at 3200 μ g/plate. Positive controls were functional. No increase in revertant colonies. **Acceptable.** (Green and Gee, 3/10/03).

****51626-019 186452,** "Gene Mutation in Chinese Hamster V79 Cells", (A. H. Seeberg and R. Forster, Life Science Research, Roma Toxicology Centre, Rome, Italy, LSR-RTC Report No. 162002-M-06985, 22 August 1985). Chinese hamster V79 cells were exposed in triplicate (2 trials) to Ethofenprox (MTI-500) (96.3% purity) in the presence and absence of rat liver S9 activation at 0 (1% dimethylsulfoxide), 9.75, 19.5, 39.0, 78.0, and 156.0 μ g/ml (limit of solubility) for three hours. No increase in mutation frequency for 6-thioguanine resistance. **Acceptable.** (Green and Gee, 3/10/03).

**51626-019 186459, "Unscheduled DNA Synthesis in Human Cells, Cell Line: HeLa S3". (A.H. Seeborg and R. Forster, Life Science Research, Rome, Italy, LSR-RTC Report No. 162003- M-05785, 30 July 1985). Human HeLa S3 cells were exposed to ethofenprox (MTI-500) (96.3%) triplicate monolayer cultures at 0 (DMSO), 2.44, 4.88, 9.75, 19.5, and 39.0 µg/ml in the presence

DNA Damage
**51626-019 186458, "MTI-500-a-CO: Assessment of its Ability to Cause Lethal DNA Damage in Strains of *Escherichia Coli*", (J. Bootman and K. May, Life Science Research Limited, Eye, Suffolk, England, LSR Report No. 85/MTO022/504, 2 October 1985). Duplicate suspensions (2-5 x 10⁶ cells/ml) of *Escherichia coli* strains WP2, WP67, and CM871 were exposed in the presence and absence of rat liver S9 activation to MTI-500-a-CO (99.6%) at 0 (DMSO), 0 (untreated), 3200, and 10000 µg/ml for 2 and 18 hours. Bacteria were diluted and plated and the number of colonies per plate scored after 1 day at 37°C. Cell lethality was not increased in repeat experiments (WP67 and CM871). Positive controls (2-aminoanthracene and mitomycin) were efficient strains (WP67 and CM871).

**51626-019 186457, "In Vitro Assessment of the Clastogenic Activity of MTI-500-a-CO in Cultured Human Peripheral Lymphocytes", (J. Bootman et al., Life Science Research Limited, Eye, Suffolk, England, LSR Report No. 85/MTO021/711, 22 November 1985). Cultures of male human blood lymphocytes in whole blood were exposed to MTI-500-a-CO (99.6%) in triplicate at 0 (DMSO), 0 (untreated medium), 2.5, 5.0, 10.0, and 20.0 µg/ml in the absence of S9 activation and retreated (without activation) for a further 22 hours. One hundred metaphases were scored per culture. Mitotic indices were used for evidence of toxicity. No increase in structural chromosomal aberrations. Positive controls were functional. Acceptable. (Green and Gee, 3/10/03).

Chromosome Effects
**51626-019 186456, "In Vitro Assessment of the Clastogenic Activity of MTI-500, Ethofenprox, in Cultured Human Peripheral Lymphocytes", (J. Bootman, et al., Life Science Research Limited, Eye, Suffolk, England, LSR Report No. 85/MTO017/430, 17 July 1985). Triplicate cultures of male human blood lymphocytes were exposed to ethofenprox (MTI-500) (96.3%) at 0 (DMSO), 6.25, 12.5, 25.0, and 50.0 µg/ml in the absence of rat liver S9 activation for 2 and 24 hours respectively (activated cultures were washed after 2 hours, then retreated for a further 22 hours). Triplicate cultures with 100 metaphases activated per culture. Mitotic indices were recorded. Positive controls were functional. No increase scored per culture. Mitotic indices were recorded. Positive controls were functional. No increase in structural chromosomal aberrations. Acceptable. (Green and Gee, 3/10/03).

**51626-019 186455, "MTI-500, Ethofenprox: Assessment of Clastogenic Action on Bone Marrow Erythrocytes in the Micronucleus Test", (J. Bootman, et al., Life Science Research Limited, Eye, Suffolk, England, LSR Report No. 85/MTO016/406, 3 July 1985). 15 (control and high dose) or 5 CD-1 mice per sex per group received a single oral gavage dose of ethofenprox (MTI-500) at 0 (0.5% methylcellulose), 80, 400, and 2000 mg/kg. Further lots of 5 animals per sex from the control and high dose groups were sacrificed 48 and 72 hours post-dosing. Approximately 2000 erythrocytes were scored per animal. The positive control, chlorambucil, was functional. No increase in micronucleated polychromatic erythrocytes. Acceptable. (Green and Gee, 3/10/03).

DN A Damage
**51626-019 186458, "MTI-500-a-CO: Assessment of its Ability to Cause Lethal DNA Damage in Strains of *Escherichia Coli*", (J. Bootman and K. May, Life Science Research Limited, Eye, Suffolk, England, LSR Report No. 85/MTO020/433, 19 July 1985). *Salmonella typhimurium* strains TA 97A, TA 98, TA 100, TA 102, TA 1535, and TA 1537 and *Escherichia coli* strain WP2 UVRA were exposed, in triplicate, in the presence and absence of rat liver S9 activation, to MTI-500-a-CO (99.6% purity) at 0 (DMSO), 50, 158, 500, 1582, and 5000 µg/ml in the presence of mutagen frequency. Positive controls were functional.

of rat liver S9 mix and at 0 (DMSO), 9.75, 19.5, 39.0, 78.0, and 156 $\mu\text{g}/\text{ml}$ without S9 for 3 hours in the presence of [^3H] thymidine in two trials. The highest concentration was based on toxicity and solubility. Replicative DNA synthesis was suppressed in arginine free medium and by hydroxyurea during exposure. DNA was extracted from cell pellets by trichloroacetic acid precipitation followed by hydrolysis in 0.3 M KOH with heating. Label incorporation was determined by LSC and DNA concentration by a colorimetric assay. Results were expressed as DPM/ μg DNA. Positive controls (4-NQO and B(a)P) were functional. No increase in unscheduled DNA synthesis. **Acceptable.** (Green and Gee, 4/9/03).

STUDIES ON METABOLITES

005; 186415; "MTI-500 α -Co: Acute Toxicity Study in the Rat" (Cummins, H.A. and Gardner, J.R., Life Science Research Limited, Eye, Suffolk, England, Laboratory Project ID 85/MT0018/474, 8/2/85). MTI-500 α -Co (Batch OFU-1021, purity = 99.6%), suspended in maize oil, was administered as a single gavage dose to 5 CD rats (remote Sprague-Dawley origin) per sex at a dose level of 5000 mg/kg. No mortalities occurred. Decreased motor activity was observed in all animals 2 hours after dosing clearing in all animals 4 hours after dosing. Necropsy revealed dark submandibular salivary glands in 2 males and large cervical lymph nodes in 1 male. LD_{50} (M/F) > 5000 mg/kg. NOEL not determined. **Supplemental study** (the test material used in the study was not the active ingredient in review) (Corlett, 11/6/02)

005; 186416; "Ethofenprox (MTI-500) Acute Limit Test of Toxicity to Dogs Following a Single Oral Administration" (Harling, R.J. et al., Department of Dog Toxicology, Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, England, Laboratory Project ID MTC 101/851185, 10/24/85). Ethofenprox (MTI-500) (Batch ST103, purity = 96.3%) was inserted into gelatine capsules and 1 pure-bred beagle dog per sex was dosed once with 5000 mg/kg. No mortalities occurred. Semi-soft green feces approximately 2 hours after dosing and semi-soft feces of normal color on Days 2 and 4 were observed in the male; no clinical signs were observed in the female. Small weight loss was observed in the female for 3 days following dosing and at the end of the 14 day observation period. Necropsy revealed no treatment-related abnormalities. Bone marrow smears taken from each animal prior to terminal sacrifice were found to be normal in cellularity, morphology, and cell distribution. LD_{50} (M/F) > 5000 mg/kg. NOEL not determined. **Supplemental study** (only 1 animal per sex per dose group used) (Corlett, 11/6/02)

CONCLUSIONS: Do data support registration?

Toxicity data were submitted to support a Section 3 registration request for Etofenprox Technical for manufacturing use only.

The acute oral and dermal toxicity and primary dermal and ocular irritation studies are acceptable. In contrast, the inhalation toxicity study is unacceptable but possibly upgradeable with submission of additional data to eliminate the deficiencies indicated in the one-liner above. MTI-500 is not a potential dermal sensitizer as indicated by the dermal sensitization study. Acceptable acute studies were submitted for a formulated product, Zoecon F254-87-1 Aerosol.

Subchronic oral feeding studies with rodents and 28-day repeated dose dermal toxicity studies are acceptable. However, the 90-day inhalation study in rats is unacceptable but may be upgradeable with submission of data and calculations used to determine the reported mean analytical concentrations of the test material.

Animal metabolism studies in dogs and rats were submitted. Collectively, the data fulfills the current requirements for an acceptable metabolism study.

Chronic feeding studies in rodents (rats and mice) and dogs are acceptable.

The data reviewed are inadequate for a complete toxicological evaluation. The acute inhalation toxicity study is unacceptable but possibly upgradeable with submission of additional data to eliminate the deficiencies indicated in the one-liners. The 90-day inhalation study is acceptable but may be upgradeable with submission of data and calculations used to determine the reported mean analytical concentrations of the test material.

Registration is not recommended at this time.

Acceptable studies were submitted to satisfy the current data requirements for gene mutation, chromosomal effects and DNA effects.

RECOMMENDATIONS: What type of registration action is being considered? In the case of ongoing registration, register or do not register? What other specific studies or data are requested?

Submitted as a Section 3 registration request for manufacturing use only.

The rat and rabbit developmental and reproduction studies are acceptable.

Acceptable studies were submitted to satisfy the current data requirements for gene mutation,

chromosomal effects and DNA effects.

TO: Steve Rhodes, Senior Pesticide Use Specialist
Pesticide Registration Branch

FROM: Medical Toxicology Branch

Original Date: 4/21/03
Revised: 7/28/03
Revised: 9/16/03
Revised: 12/5/03

PRODUCT REGISTRATION RECOMMENDATION SHEET

Formulated Product Name: Etofenprox Technical

Chemical Code #: 2292

ID #: 193825N

EPA Reg. #: 33657-6

SB 950 #: NA

Document #: 51626- 002, -005 to - 013, and -016 to -020, -023 to -0025

Company Name: Mitsui Chemicals, Inc.

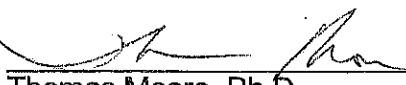
RECOMMENDATION:

Submitted as a Section 3 registration request for manufacturing use only.

The data reviewed are adequate for a complete toxicological evaluation.

The product label adequately identifies the acute toxicity hazards indicated by the data reviewed.

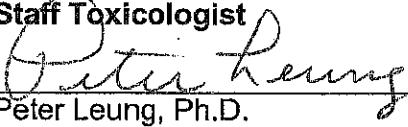
Registration is recommended. In accordance with DPR policy, the risk assessment on the active ingredient will be conducted after registration as prioritized by the SB950 Adverse Effects Advisory Panel (see memorandum of 8/22/96).



Thomas Moore, Ph.D.

12-8-03

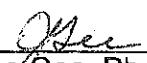
Date



Peter Leung, Ph.D.

12/8/03

Date



Joyce Gee, Ph.D.
Senior Toxicologist

12/8/03

Date

DATA PACKAGE SUMMARY AND RECOMMENDATION SHEET - NEW ACTIVE INGREDIENT

FROM: **Medical Toxicology Branch** 12/5/03

TO: **Steve Rhodes, Registration Specialist**
Pesticide Registration Branch

DRR MEDICAL TOXICOLOGY
D51626-S193825C
Page 2

SUMMARY ("One-liners" from each study worksheet, significant information not mentioned in worksheets, other pertinent information for ongoing review or registration.)

Attach additional sheets if needed)

Submitted for manufacturing use only. Etofenprox is also known as MTI-500.

ACUTE STUDIES - Technical

Toxicity Category

Acute Oral Toxicity LD ₅₀	IV	Primary Eye irritation	Not a sensitizer
Acute Inhalation Toxicity LC ₅₀	IV	Primary Dermal Irritation	
Acute Dermal Toxicity LD ₅₀	III		
Acute Oral Toxicity LD ₅₀	IV		
002; 068280, "Report on Acute Toxicity Study of MTI-500 (Etofenprox) in Rats" (Hashimoto, K., Hatanou Research Institute, FDSC, Hatanou, Kanagawa, Japan, Project No. A-82-27~34, 10/21/82).			
811. MTI-500 (Lot # ST-101, purity = 96%), warmed in a water bath and administered as a single gavage dose to 10 ICR mice per sex per dose levels of 53.60 and 107.20 g/kg. Mortalities occurred as follows: males: 1/10, 0/10, respectively; females: 1/10, 1/10, respectively. Water diarrhea was observed in all animals beginning 15-20 minutes after dosing with hair around the anus markedly soiled. At 24 hours, soft yellowish stools and anal prolapse were observed in some animals; abdominal swelling, piloerection, facial edema, and soiling of hair over the entire body were also observed. Diarrhea ceased 48 hours after dosing. Necropsy revealed no treatment- related effects.			

002; 068281, "Report on Acute Toxicity Study of MTI-500 (Etofenprox) in Mice" (Hashimoto, K., Hatanou Research Institute, FDSC, Hatanou, Kanagawa, Japan, Project No. A-82-35~42, 10/21/82).			
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related abnormalities. LD₅₀ (M/F) > 107.20 g/kg. NOEL not determined. Toxicity Category IV. **Acceptable.** (Corlett, 11/4/02)

Acute Dermal Toxicity

002; 068280; "Report on Acute Toxicity Study of MTI-500 (Ethofenprox) in Rats" (Hashimoto, K., Hatano Research Institute, FDSC, Hatano, Kanagawa, Japan, Project No. A-82-27~34, 10/21/82). 812. MTI-500 (Lot # ST-102, purity = 96%), warmed in a water bath and applied to the clipped skin of 10 Sprague-Dawley rats per sex per dose at a dose level of 2.144 g/kg for 24 hours. No mortalities occurred. Crouching and a reduction in spontaneous movement were observed in all animals 1 or 2 hours after application. Necropsy revealed no treatment-related abnormalities. Reported LD₅₀ (M/F) > 2.144 g/kg. Toxicity Category not determined. **Unacceptable but possibly upgradable** with submission of information detailing how the test article was held in contact with the skin during the exposure period. (Corlett, 11/4/02)

002; 068281; "Report on Acute Toxicity Study of MTI-500 (Ethofenprox) in Mice" (Hashimoto, K., Hatano Research Institute, FDSC, Hatano, Kanagawa, Japan, Project No. A-82-35~42, 10/21/82). 812. MTI-500 (Lot # ST-102, purity = 96%), warmed in a water bath and applied to the clipped skin of 10 ICR mice per sex per dose at dose levels of 1.072 and 2.144 g/kg for 24 hours. No mortalities occurred. No clinical signs were observed. Necropsy revealed no treatment-related abnormalities. Reported LD₅₀ (M/F) > 2.144 g/kg. Toxicity Category not determined. **Unacceptable but possibly upgradable** with submission of information detailing how the test article was held in contact with the skin during the exposure period. (Corlett, 11/4/02)

51626-0023; 205045; "Acute Dermal Toxicity Study of Etofenprox in Rats"; (S. Oda; Bozo Research Center, Inc., Gotemba Laboratory, Setagaya-ku, Tokyo 156-0042, Japan; Project ID. B-5040; 2/5/03); The skin of five Sprague-Dawley (Crj:CD(SD)IGS) rats/sex was treated with 0 or 2000 mg/kg of etofenprox technical (lot. no. 20024, purity: 99.0%) for 24 hours under an occlusive wrap. No deaths resulted from the treatment. No treatment-related clinical signs were evident. In the necropsy examination, no treatment-related lesions were noted. LD₅₀ (M/F) > 2000 mg/kg; Toxicity Category III; **Study acceptable.** (Moore, 7/25/03)

Acute Inhalation Toxicity

51626-002, -0025; 68282, 208111; "MTI-500 Acute Inhalation Toxicity in Rats 4 Hour Exposure" (Jackson, G.C. et al., Huntingdon Research Centre, Huntingdon, Cambridgeshire, England, HRC Report No. MTC 60/821079, 4/2/86 (re-issue)). 813. MTI-500 (Lot No. ST-101, purity = 96%) was blended with acetone, aerosolized, and administered in a whole body manner to 5 COBS® rats per sex at a dose level (mean analytical concentration) of 5.9 mg/l (95% of the test material < 5.5 µm aerodynamic diameter) for 4 hours. No mortalities occurred. Treatment-related clinical signs included closing or partial closing of eyes and dyspnea during exposure, and oily fur, lethargy, hair loss (females only), and hyperactivity during the 14 day observation period. Necropsy revealed no treatment-related abnormalities except for a black area on the liver of 1 male. LC₅₀ (M/F) > 5.9 mg/l. Toxicity Category IV. **Previously Unacceptable but possibly upgradable** with a clarification on the amount of acetone blended with the test material and the submission of the data and calculations used to determine the mean analytical concentration of the test material; the data submitted in vol. 51626-0025, rec. no. 208111 were sufficient to document the analytical exposure concentrations reported in the study. **Study acceptable.** (Corlett, 10/10/02), revised, Moore, 12/5/03)

Primary Eye Irritation

002; 068285; "MTI-500 Primary Ophthalmic Stimulation Test in Rabbits" (Kashima, M., Haruna Laboratory, Nippon Experimental Medical Research Institute, Ltd., Agatsuma-gun, Gunma Prefecture, Japan, Project No. Nemri-H-85-55, 10/24/85). 814. 0.1 ml of MTI-500 (Lot No. ST-103, purity = 96.3%) was placed into the conjunctival sac of 1 eye of each of 6 Japanese White rabbits. No corneal opacity or iritis was observed in any treated eye. Grade 1 conjunctival irritation was observed in 5 of 6 treated eyes 24 hours after treatment with all signs of conjunctival irritation

Primary Dermal Irritation

002; 068284; "MTI-500 Primary Skin Stimulation Test in Rabbits" (Kashima, M., Haruna Prefecture, Nippon Experimental Medical Research Institute, Ltd., Agatsuma-gun, Gunma Prefecture, Japan, no study or project number provided, 10/31/85). 816. A modification of MTI-500 (Lot No. ST-103, purity = 96.3%) was applied to the clipped and shaved skin of the back of 6 Japanese white rabbits for 4 hours using a semi-occlusive wrap. No edema was observed at any test site. Grade 1 erythema was first observed in 1 animal 48 hours after patch removal. Persistence through 7 days after patch removal and clearing 8 days after patch removal. Toxicity Category IV. Acceptable. (Corlett, 10/24/02)

Dermal Sensitization

002; 068283; "MTI-500 Skin Sensitization Test in Guinea Pigs" (Kobayashi, K., Oizumi Laboratory, Nippon Experimental Medical Research Institute, Ltd., Ohta-gun, Gunma Prefecture, Japan, no study or project number provided, 10/31/85). 816. A modification of MTI-500 (Lot No. ST-103, purity = 96.3%) to elicit delayed contact hypersensitivity in the guinea pig. 20 English Hartsley guinea pigs were treated with the test material during the induction phase (intradermal injection following the topical induction dose). A concurrent negative control group consisting of 20 animals followed 7 days later by a topical application. The control animals were treated identically to the test animals except that during induction the test material was replaced with vehicle. Observations 24, 48, and 72 hours after the challenge did not indicate any skin-sensitization reaction. Positive controls in the frequency of respiration, and coughing were observed immediately after dosing at both 16.08, and 32.16 g/kg. At 32.16 g/kg, the injection site was markedly swollen with test article leakage in some animals. A blood-like substance on the eyelids or nostrils and grayish-white soft stools, swelling of the dorsal neck, and edema over the dorsal neck down to the forelegs were observed in all animals, along with hair soiled by oily dirt and scar formation or depilation at the injection site in some animals. Histopathological examination revealed the fluid in the subcutaneous tissue dorsal neck and granulation tissue formed around the fluid in the subcutaneous tissue of the viscous liquid and granulation tissue in some animals. Histopathological examination revealed the fluid in pale yellow solution in all animals, along with hair soiled by oily dirt and scar formation or depilation at the injection site in a water bath and administered subcutaneously into the interscapular region of the dorsum of 10 ICR mice per sex per dose at dose levels of 26.80 and 53.60 g/kg and observed for 14 days. No mortalities occurred. Swelling at the test site (in all animals) and scaling of the hair at the test site (in some animals at 53.60 g/kg) were observed. Histopathological examination of test material at the test site and granuloma formation in the subcutaneous connective tissues at the test site, LD₅₀ (M/F) > 53.60 g/kg. NOEL not determined. Supplemental study (not a guideline study) (Corlett, 11/4/02)

SUPPLEMENTAL

002; 068281; "Report on Acute Toxicity Study of MTI-500 (Ethofenprox) in Mice" (Hashimoto, K., Hatano Research Institute, FDS-C, Hatano, Kanagawa, Japan, Project No. A-82-35-42, 10/21/82). MTI-500 (Lot # ST-101, purity = 96%), warmed in a water bath and administered subcutaneously into the interscapular region of the dorsum of 10 ICR mice per sex per dose at dose levels of 26.80 and 53.60 g/kg and observed for 14 days. No mortalities occurred. Swelling at the test site (in all animals) and scaling of the hair at the test site (in some animals at 53.60 g/kg) were observed. Histopathological examination of test material at the test site and granuloma formation in the subcutaneous connective tissues at the test site, LD₅₀ (M/F) > 53.60 g/kg. NOEL not determined. Supplemental study (not a guideline study) (Corlett, 11/4/02)

002; 068280; "Report on Acute Toxicity Study of MTI-500 (Ethofenprox) in Rats" (Hashimoto, K., Hatano Research Institute, FDSC, Hatano, Kanagawa, Japan, Project No. A-82-27~34, 10/21/82). MTI-500 (Lot # ST-101, purity = 96%), warmed in a water bath and administered intraperitoneally to 10 Sprague-Dawley rats per sex per dose at dose levels of 21.44 and 42.88 g/kg and observed for 14 days. No mortalities occurred. Piloerection and crouching with hollowed belly were observed immediately after dosing at both 21.44 and 42.88 g/kg. Diarrhea or soft stools were observed in all animals the day after test article administration. Necropsy revealed whitish yellow granules adhering to various organs in the abdomen including the fat tissue of the abdominal wall, omentum and mesenterium and around the testes in all animals; hemorrhagic points scattered in the lungs, congestion of the liver, and minor granuloma on the serous membrane of the liver and spleen and on the parietal peritoneum were also observed. LD_{50} (M/F) > 42.88 g/kg. NOEL not determined. **Supplemental study** (not a guideline study) (Corlett, 11/4/02)

002; 068281; "Report on Acute Toxicity Study of MTI-500 (Ethofenprox) in Mice" (Hashimoto, K., Hatano Research Institute, FDSC, Hatano, Kanagawa, Japan, Project No. A-82-35~42, 10/21/82). MTI-500 (Lot # ST-102, purity = 96%), warmed in a water bath and administered intraperitoneally to 10 ICR mice per sex per dose at dose levels of 6.70, 13.40, 26.80, and 53.60 g/kg and observed for 21 days. Mortalities occurred as follows- males: 2/10, 3/10, 4/10, 3/10, respectively; females: 0/10, 1/10, 7/10, 7/10, respectively. 15 minutes after dosing, reduced appetite and reduced spontaneous movements were observed at all dose levels. 1 day after dosing, piloerection, facial edema, abdominal swelling, and soft stools were observed. Histopathological examination revealed the formation of minor granuloma in the serous membranes of liver, spleen, pancreas, and digestive tract. LD_{50} (M/F) not determined. NOEL not determined. **Supplemental study** (not a guideline study) (Corlett, 11/4/02)

ACUTE STUDIES - Zoecon F254-87-1 Aerosol

	Toxicity Category
Acute Oral Toxicity LD50	IV
Acute Dermal Toxicity LD50	III
Acute Inhalation Toxicity LC50	IV
Primary Eye Irritation	IV
Primary Dermal Irritation	III
Dermal Sensitization	Not a sensitizer

Acute Oral Toxicity

002; 068288; "Acute Oral Toxicity Study in Rats Administered Test Article Zoecon F254-87-1 Aerosol, Lot No. L255-140-1" (Davis, T.K., UBTL, Inc., Salt Lake City, UT, Study #63296, 5/8/87). 811. Zoecon F254-87-1 Aerosol (Lot No. L255-140-1, 1.3% etofenprox, 0.38% (S)-hydroprene) was administered as a single gavage dose to 5 Sprague Dawley rats per sex per dose at a dose level of 5.1 g/kg. No mortalities occurred. Nasal discharge was observed in 2 animals on the day of dosing clearing in both animals on the next day. Necropsy revealed kidneys exhibiting light red to dark red mottled appearance in 1/5 males and in 2/5 females and each kidney exhibiting 2-12 infarcts in 3/5 males and 3/5 females. LD_{50} (M/F) > 5.1 g/kg. Toxicity Category IV. **Acceptable.** (Corlett, 10/30/02)

Acute Dermal Toxicity

002; 068287; "Acute Dermal Toxicity Study in Rabbits Administered Test Article Zoecon F254-87-1 Aerosol, Lot No. L255-140-1" (Davis, T.K., UBTL, Inc., Salt Lake City, UT, Study #63297, 5/8/87). 812. Zoecon F254-87-1 Aerosol (Lot No. L255-140-1, 1.3% etofenprox, 0.38% (S)-hydroprene) was applied to the clipped skin of 5 New Zealand White rabbits per sex per dose at a dose level of 2.1 g/kg for 24 hours. No mortalities occurred. No treatment-related clinical signs were observed. Erythema was observed in all animals after patch removal; edema and eschar were also observed in some animals. Necropsy revealed dry skin at the exposure site in 1 male

Acute Inhalation Toxicity

002; 068286, "The Acute Toxicity of Inhaled Zoecon F254-87-1 Aerosol (Lot No. L255-149-1) in the Albino Rat (Safety Test)" (Vau, A. et al., Bio-Research Laboratories Ltd., Senneville, Quebec, Canada, Project No. 82969, 6/8/87). 813. F254-87-1 Aerosol (Lot No. L255-149-1, 1.3% etofenprox, 0.4% (S)-hydroprene) was aerosolized and administered in a whole body manner to 5 CH₂CD₃(SD)BR rats per sex at a dose level (mean gravimetric concentration) of 4.32 mg/l (mean mass median particle diameter (GSD) of 3.5 (2.0) μ m) for 4 hours. No mortalities occurred. Treatment-related clinical signs included partial closing of eyes, inactivity, and slightly wet fur during exposure, and red muzzles staining, pale eye color, dociility, and rough and wet fur after exposure; all signs cleared the next day. Necropsy revealed no treatment-related abnormalities. LC_{50} (M/F) > 4.32 mg/l. Toxicity Category IV. Acceptable. (Corlett, 10/29/02)

Primary Eye Irritation

002; 068291, "Primary Eye Irritation Study in Rabbits Administered Test Article Zoecon F254-87-1 Aerosol, Lot No. L255-140-1" (Davis, T.K., UBTL, Inc., Salt Lake City, UT, Study #63298, 5/8/87). 814. A single 1 second burst from a distance of approximately 10 cm of Zoecon F254-87-1 Aerosol (Lot No. L255-140-1, 1.3% etofenprox, 0.38% (S)-hydroprene) was administered to 1 eye of each of 9 New Zealand White rabbits. 3 of the treated eyes were washed and 6 were not washed. No corneal opacity or irritants was observed in any unwashed treated eye. Grade 1 conjunctival irritation was observed in 3 of 6 unwashed treated eyes 1 hour after treatment with all rabbits for 4 hours. Grade 2 erythema was observed in all animals 7 days after patch removal, decreasing to grade 1 in 2 animals and grade 1 in 4 animals 7 days after patch removal, decreasing to grade 2 in 3 animals 14 days after patch removal. Grade 1 edema was observed in 3 animals 24 hours after patch removal and in 1 animal 72 hours after patch removal with all signs of edema clearing in all animals 7 days after patch removal. Toxicity Category III.

Primary Dermal Irritation

002; 068289, "Primary Dermal Irritation Study in Rabbits Administered Test Article Zoecon F254-87-1 Aerosol, Lot No. L255-140-1" (Davis, T.K., UBTL, Inc., Salt Lake City, UT, Study #63298, 5/8/87). 815. 0.5 ml of Zoecon F254-87-1 Aerosol (Lot No. L255-140-1, 1.3% etofenprox, 0.38% (S)-hydroprene) was applied to each of 2 sites on the clipped skin of each of 6 New Zealand rabbits for 4 hours. Grade 2 erythema was observed in all animals 7 days after patch removal, decreasing to grade 2 in 2 animals and grade 1 in 4 animals 7 days after patch removal, decreasing to grade 1 in 3 animals 14 days after patch removal. Grade 1 edema was observed in 3 animals 24 hours after patch removal and in 1 animal 72 hours after patch removal with all signs of edema clearing in all animals 7 days after patch removal. Toxicity Category III.

Dermal Sensitization

002; 068290, "Dermal Sensitization Study in Albino Guinea Pigs Administered Test Article Zoecon F254-87-1 Aerosol, Lot No. L255-140-1" (Davis, T.K., UBTL, Inc., Salt Lake City, UT, Study #63300, 5/8/87). 816. A modified version of the Buehler method was used to assess the skin sensitization potential of Zoecon F254-87-1 Aerosol (Lot No. L255-140-1, 1.3% etofenprox, 0.38% (S)-hydroprene). 10 Hartley albino guinea pigs were treated with the test material. Each animal shaved area for 6 hours, 1 application per week for 3 weeks (3 total applications). Each animal shaved area for 6 hours, 1 application per week for 3 weeks (3 total applications). Each animal was then challenged with the same induction dose for 6 hours. The test material produced a positive result in 20% of the treated animals 48 hours after challenge. Positive controls fumigated. The results of this study indicate that the test material is a potentinal contact sensitizer when using this modified version of the method of Buehler. Acceptable. (Corlett, 11/4/02)

SUBCHRONIC STUDIES

(Oral)

007; 186424; "Assessment of the Toxicity of MTI-500 in Rats by Dietary Administration for 13 Weeks" (Green, O.P. et al., Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, England, Laboratory Project ID MTC 56/821067/2, 4/2/86). 821. MTI-500 (Batch No. ST-101, purity = 96%) was admixed to the diet and fed to 20 CD rats per sex per dose at dose levels of 0 (diet and corn oil only), 50, 300, 1800, or 10800 ppm (0, 3.3, 20, 120, 734 mg/kg/day, respectively, for males and 0, 3.8, 23, 142, 820 mg/kg/day, respectively, for females) for 13 weeks. No treatment-related mortalities occurred. No treatment-related clinical signs were observed. A treatment-related decrease in mean thyroxine (T_4) levels in males at 1800 and 10800 ppm was observed. Treatment-related increases in mean adjusted liver weight in males at 10800 ppm and in females at 1800 and 10800 ppm and mean adjusted thyroid weight in males at 1800 and 10800 ppm were observed. Microscopic examination revealed an increased incidence of microfollicles in the thyroid in males at 1800 and 10800 ppm and in females at 10800 ppm and enlargement of the centrilobular hepatocytes in females at 10800 ppm. **No adverse effects.** NOEL (M) = 20 mg/kg/day (300 ppm) based on an increased incidence of microfollicles in the thyroid, NOEL (F) = 23 mg/kg/day (300 ppm) based on increased liver weights and enlargement of the centrilobular hepatocytes. **Acceptable.** (Corlett, 11/22/02)

006; 186423; "Assessment of the Toxicity of MTI-500 to Mice by Dietary Administration for 13 Weeks" (Green, O.P. et al., Huntingdon Research Centre plc, Huntingdon, Cambridgeshire, England, Laboratory Project ID MTC 55/821112/2, 4/2/86). 821. MTI-500 (Batch No. ST-103, purity = 96%) was admixed to the diet and fed to 20 CD-1 mice per sex per dose at dose levels of 0 (diet and corn oil only), 50, 500, 3000, or 15000 ppm (0, 6.1, 60, 375, 1975 mg/kg/day, respectively, for males and 0, 6.9, 71, 390, 2192 mg/kg/day, respectively, for females) for 13 weeks. 2 males and 6 females at 15000 ppm died or were killed for humane reasons and these deaths are considered treatment-related. At 15000 ppm, treatment-related piloerection, hunched posture, emaciated and/or anemic appearance, body tremors, and respiratory distress in both sexes, and lethargy and unsteady gait in females were observed. Treatment-related decreased body weight gain and increased water consumption were observed in both sexes at 15000 ppm. Treatment-related increases in mean urea nitrogen and cholesterol levels and in mean relative liver and kidney weights were observed in both sexes at 15000 ppm. Macroscopic examination revealed kidneys that were pale, enlarged, and with cortical scarring in both sexes at 15000 ppm. Microscopic examination revealed kidneys with widespread tubular basophilia, extensive tubular dilatation, and dilatation of the renal pelvis, centrilobular hepatocyte enlargement, increased cellularity of splenic white pulp, and lymphoid hyperplasia in both sexes at 15000 ppm. **No adverse effects.** NOEL (M) = 375 mg/kg/day (3000 ppm), NOEL (F) = 390 mg/kg/day (3000 ppm) based on kidneys with widespread tubular basophilia and extensive tubular dilatation. **Acceptable.** (Corlett, 11/18/02)

(Dermal)

008; 186425; "A 28-Day Repeated Dose Dermal Toxicity Study in Rabbits with Technical MTI-500" (Killeen, J.C., Jr., Toxicology & Metabolism, Ricerca, LLC, Painesville, OH, Document No. 011077-1, 6/28/00). 870.32. Technical MTI-500 (Lot No. 21049, purity = 99.18%) was applied to the clipped dorsal skin of 10 New Zealand White rabbits per sex per dose at dose levels of 0 (tap water only), 400, 650, or 1000 mg/kg/day for 6 hours per day, for 28 consecutive days. In addition, 10 animals per sex at the control and high dose levels were used to assess recovery (recovery group animals were observed for an additional 2 weeks after the others were sacrificed). No mortalities occurred. No treatment-related systemic clinical signs were observed. Body weight and organ weight determinations along with hematology and serum chemistry revealed no treatment-related effects. Treatment-related erythema at the test site was observed at the 400, 650 and 1000 mg/kg/day dose levels in both sexes throughout the 28-day treatment period. Microscopic examination revealed treated skin where the epidermis exhibited treatment-related diffuse hyperplasia at 400, 650, and 1000 mg/kg/day in both sexes; treated recovery group animals did not significantly exhibit this effect. **No adverse effects.** NOEL (M/F, systemic) = 1000

mg/kg/day based on no treatment-related effects at the highest dose tested; NOEL (M/F, skin) < 400 mg/kg/day based on incidences of erythema and epidermis with diffuse hyperplasia.

Acceptable. (Corlett, 12/1/02)

51626-009, -0025; 186426, 208112; "Ethofenprox (MTI-500) 90-Day Inhalation Study in Rats" (inhalation) (Goombs, D.W., et al, Huntingdon Research Centre Ltd, Huntingdon, Cambridgeshire, England, Laboratory Project ID MTC 81/841257, 8/23/85). 824. Ethofenprox (MTI-500, Batch No. ST 103, Purity = 96%) was mixed with acetone (90% ester triclc: 10% acetone, w/w), aerosolized, and administered in a whole-body manner to 15 Wistar rats per sex at dose levels (mean analytical concentration at the high dose level), 0 (air control), 0.042, 0.21, 1.01 mg/l (with an average of 90.1% to 90.9% of the test material < 5.5 μ m equivalent aerodynamic diameter) for 6 hours per day 6 days per week for 13 consecutive weeks. No mortalities were reported. Treatment-related scab formation at the back of the ears was observed in males at 1.01 mg/l and in females at 0.21 and 1.01 mg/l. mean adrenal weight in females at 0.21 and 1.01 mg/l were observed. Microscopic examination revealed minimal enlargement of adrenals in both sexes at 1.01 mg/l, a minimally increased number of microfollicles and minimally increased height of follicular epithelium in the thyroid in males at 1.01 mg/l, and a minimally increased cortical width of adrenals in females at 0.21 and 1.01 mg/l. NOEL (F) = 0.042 mg/l based on enlarged adrenals and increased adrenal weight together increased weights together a minimal enlargement of central hilar hepatocytes and a minimally thyroid weight in males per sex received a single oral average dose of ^{14}C -Ethofenprox at 30 mg/kg. Two Beagle dogs per sex received a single oral average dose of ^{14}C -Ethofenprox 11 October 1985). Huntingdon, Cambridgeshire, England, HRC Report No. HRC/MTC 69/84583, 11 October 1985). Department of Chemical Metabolism and Radionuclides, Huntingdon Research Centre, et al., **51626-020 186460, "The Metabolism of ^{14}C -Ethofenprox in Dogs", (D.R. Hawkins, et al., Metabolism

METABOLISM STUDIES

thyroid; NOEL (F) = 0.042 mg/l based on enlarged adrenals and increased adrenal weight together with adrenals with a minimally increased cortical width. Previously unacceptable but possibly upgradeable with the submission of the test material, Study acceptable. (Corlett, 12/3/02, revised, Moore 12/5/03)

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**51626-020 186461, "The Biokinetics and Metabolism of ¹⁴C-Ethofenprox in the Rat", (D. R. Hawkins, et al., Department of Chemical Metabolism and Radiosynthesis, Huntingdon Research Centre, Huntingdon, Cambridgeshire, England, HRC Report No. MTC 68/84610, 1 August 1985). Single (30 and 180 mg/kg) and multiple (30 mg/kg/day for 7 or 14 consecutive days) doses of ¹⁴C-ethofenprox were used for groups of 3, 5, or 25 CD rats per sex or 3 or 10 pregnant/lactating females per group to evaluate metabolic and pharmacokinetic parameters.

A single oral dose of ¹⁴C-ethofenprox at 30 mg/kg to 5 rats per sex was mainly eliminated in the feces. During the 5 days following dosing, means of 88.0% and 86.4% dose were excreted by males and females respectively by this route. Approximately equal amounts (35% to 40% of dose) were excreted by both sexes during the 0 to 24 hour and 24 to 48 hour periods. Excretion of radioactivity in the urine accounted for means of 10.8% (males) and 8.0% (females) over 5 days and most was excreted in the first 24 hours. Mean total retention of radioactivity in the bodies 5 days post-dosing was 3.4% (males) and 3.5% (females). The pattern of excretion of radioactivity after a single oral dose of ¹⁴C-ethofenprox to 5 per sex at 180 mg/kg was similar to that seen at 30 mg/kg. Tissue concentrations of radioactivity were measured at 120 hours after dosing. Highest mean tissue concentrations were found in fat of 30 mg/kg dosed animals (16.6 µg/g in males, 11.1 µg/g in females). Muscle concentrations were near the limit of accurate measurement (0.05 µg/g). Liver contained mean concentrations of 0.34 µg/g (males) and 0.33 µg/g (females). Mean kidney concentrations were 0.13 and 0.16 µg/g for males and females respectively. At 180 mg/kg, mean fat concentrations of radioactivity were 90.2 µg/g and 94.0 µg/g for males and females respectively 120 hours after dosing. Concentrations in other tissues were all below 2 µg/g. Unchanged ethofenprox accounted for 6.6% and 14.0% of dose for males and females respectively at 30 mg/kg, and, for 22.6% and 29.0% respectively at 180 mg/kg in extracts of rat feces collected during 72 hours. The metabolite desethylethofenprox was 19.5% (males) and 25.1% (females) at 30 mg/kg and 23.2% and 20.6% respectively at 180 mg/kg over the same time period. Another metabolite, 4'-hydroxyethofenprox, made up 13.2% and 13.8% at 30 mg/kg and 7.2% and 8.1% at 180 mg/kg of the extracts for males and females respectively.

After a single oral dose at 30 mg/kg to 5 per sex, peak plasma concentrations (approximately 5 µg/ml) occurred 2 to 7 hours later. Peak plasma concentrations (16 µg/ml to 17 µg/ml) were reached 5 hours post-dosing after a single dose of 180 mg/kg.

In a tissue distribution assay, 30 mg/kg/day of ¹⁴C-ethofenprox was administered to 25 rats per sex on seven consecutive days. 5 per sex were sacrificed for sampling at 4, 24, 48, 120, and 240 hours after the last dose. The highest concentrations of radioactivity in all tissues were found at 4 hours post-dosing. Fat contained the highest concentration (94.2 µg/g to 101 µg/g). Next highest concentrations (30.5 µg/g male, 22.3 µg/g female) were found in liver at 4 hours. The major component in fat and liver was unchanged ethofenprox.

10 pregnant female rats received 30 mg/kg/day of ¹⁴C-ethofenprox by oral intubation on gestation days 10 through 16. 2 dams were sacrificed for sampling at 4, 24, 48, 72, and 120 hours after the last dose. Adrenal glands, kidneys, heart, and liver showed radioactivity concentrations and patterns of elimination of radioactivity similar to non-pregnant animals. Of those, adrenal glands contained the highest concentrations, 61.5 µg/g at 4 hours, declining to 5.74 µg/g at 120 hours. Of the reproductive tissues, mammary contained the highest concentrations (87.4 µg/g at 4 hours declining to 32.4 µg/g at 120 hours after the last dose), similar to those in fat of non-pregnant animals. Radioactivity concentrations in placentae were lower than in any other maternal tissue. Concentrations declined from 4.6 µg/g to 4.8 µg/g at 4 hours to 0.17 µg/g at 120 hours. Maximum fetal concentrations were 1.6 µg/g to 1.7 µg/g at 4 hours.

Secretion of radioactivity into the milk of mother rats was evaluated by analysis of the stomach contents of suckling pups. Dams were treated with 30 mg/kg/day of ¹⁴C-ethofenprox by oral intubation from gestation day 18 through lactation day 9 (14 days total). Radioactivity concentration in pup stomach contents ranged from 41.3 µg/g to 88.3 µg/g after one hour of suckling compared to maternal plasma concentrations in the range of 1.9 µg/ml to 3.6 µg/ml. Chromatographic

**51626-020 186462, "Dermal Absorption of ^{14}C -Etofenprox in Male Rats (Preliminary and Definitive Phases)", (Fred Thalacker, Covance Laboratories, Inc., Madison, WI, Laboratory Project Number CHW 6648-135, 4 January 1999). Shaved, washed, unabraded skin of the back and shoulders (12.5 cm^2) of 16 CD BR SD male rats per group was treated (non-occlusive) once with ^{14}C -Etofenprox (MTI-500) at 5, 59, and $184 \mu\text{g}/\text{cm}^2$. 4 animals per group were sacrificed for analysis at 1, 10, 24, and 96 hours post-dosing. The skin at the application site was washed using 2% Ivory soap just before sacrifice (1-and 10-hour sacrifice animals) or 10 hours after treatment (24- and 96-hour sacrifice animals) and the wash retained. Overall recoveries of radioactivity including all time points, were 94.9%, 97.9%, and 122% of the total dose at 5, 59, and $184 \mu\text{g}/\text{cm}^2$ respectively. Most of the radioactivity (80% to 101% across groups) was found in the skin wash. The mean of applied radioactivity detected in or on skin was 4.59% to 13.5% (low dose), 7.07% to 18.1% (mid dose), and 8.52% to 30.3% (high dose). The percentage of applied radioactivity absorbed (found in blood, carcass, and excreta (urine, feces, cage wash and cage wipe)) was 5.07%, 6.10%, and 6.57% at 5, 59, and $184 \mu\text{g}/\text{cm}^2$ after 96 hours. Acceptable. (Green and Gee, 3/13/03).

analysts indicated that 95% of the radiocentric images tested by the pups was associated with unchanged ethophenprox. Acceptable. (Green and Gee, 4/10/03).

Chronic Toxicity, Dog

** 51626-010, -0024 186427, 205248, "Ethofenprox (MTI-500) Toxicity to Dogs by Repeated Dietary Administration for 52 Weeks Followed by a Recovery Period of 8 Weeks", (Robert J. Harling, et al., Huntingdon Research Centre, Ltd., Huntingdon, Cambridgeshire, England, Report # MTC 71/85234, 25 October 1985). 6 (control and high dose) or 4 Beagle dogs per sex per group received ethofenprox (MTI-500) (96.3% purity) in the diet at 0 (basal diet + corn oil), 100, 1000, and 10000 ppm for 52 weeks. In a recovery phase, 2 animals per sex from the control and high dose groups received untreated diet for 8 weeks following treatment. Mg/kg/day equivalents for males and females were 3.46 and 3.17; 33.37 and 32.19; and 351.73 and 339.32 at 100, 1000, and 10000 ppm respectively. Statistically significant decreases in total protein and cholesterol and increases in alkaline phosphatase were noted for 10000 ppm males and females from week 6 onwards. After 52 weeks of treatment; lung, liver, kidney, and pancreas weights (as % of bodyweight) were increased (statistical significance for liver) for both sexes at 10000 ppm relative to controls. One 1000 ppm female and 2 males and 1 female at 10000 ppm were noted with accentuation of the lobular markings of the liver at 52 week necropsy. Histopathology revealed 2/4 female dogs at 10000 ppm with minimal swelling of centrilobular liver cells at 52 weeks. The noted changes were generally diminished or absent after the 8 week recovery period. **No adverse effects.** **Chronic NOEL:** (M/F) 1000 ppm ((M): 33.37 mg/kg/day, (F) : 32.19 mg/kg/day) (based upon increased absolute and relative liver weights, increased serum alkaline phosphatase activity and swelling of the centrilobular liver cells in the 10000 ppm treatment group); Study previously unacceptable, possibly upgradeable with dose level justification; data submitted in vol. 51626-0024, rec. no. 205248 was sufficient to justify the dose. **Study acceptable.** (Green and Gee, 4/10/03, upgraded, Moore, 9/16/03).

Oncogenicity, Mouse

**51626-013, 016 186440, 186443, "Ethofenprox (MTI-500) Potential Tumorigenic and Toxic Effects in Prolonged Dietary Administration to Mice (Final Report)", (Owen P. Green, et al., Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, England, Report # MTC 58/85582, 6 January 1986). Seventy-six CD-1 mice (of Swiss origin) per sex per group received ethofenprox (MTI-500) technical (96.3%) in the diet at 0 (basal diet + corn oil), 30, 100, 700, and 4900 ppm for 108 weeks. Fifty-two per sex per group, designated main group animals, were treated through 108 weeks. The remaining 24 per sex per group satellite animals were used for blood and urine sampling at intervals through week 52 and for interim necropsies at 26 and 52 weeks. Mean mg/kg/day intake of ethofenprox for weeks 1 through 108 was 3.1 and 3.6, 10.4 and 11.7, 75.2 and 80.9, and 546.9 and 615.5 mg/kg/day for males and females at 30, 100, 700, and 4900 ppm respectively. For males at 4900 ppm, survival was reduced at study termination and bodyweight gain was decreased through week 52. Water consumption increased (statistically significant) for both sexes at 4900 ppm for weeks 5, 12, and 23 and urine volume was higher (statistically significant) for males at all treatment levels at week 52. Absolute (g) liver weights were higher (statistically significant) for males at 4900 ppm and relative liver weights (% bodyweight) were increased for both sexes. Also at necropsy, in both sexes, the incidence of pale kidneys was increased at 100, 700, and 4900 ppm and renal cortical scarring incidence was higher at 4900 ppm. Treatment related non-neoplastic changes were confined to the kidney. Increases in dilated/basophilic cortical tubules of varying severity were noted for both sexes at 100, 700, and 4900 ppm and for males at 30 ppm. This lesion was associated with focal loss of tubules at the higher dose levels. No carcinogenicity, no adverse effects. Chronic NOEL = 30 ppm (3.1 and 3.6 mg/kg/day in males and females respectively) (kidney changes). Record 186443 contains a photomicrography addendum for kidney changes. No evidence of oncogenicity. Acceptable. (Green and Gee, 4/2/03).

The study (record 186441) discussed the U.S. EPA classification of etofenprox as a Group C Oncogen on the basis of increased incidence (outside the historical control range for the performing laboratory) of thyroid follicular cell adenomas and adenomas/carcinomas combined in the rat. The authors requested a reclassification for etofenprox to Group D or E Oncogen based on the negative results of mice and dog studies previously conducted showing no thyroid oncogenicity. Also, on results of the *in vitro* studies (non-guideline protocols) in the appendix on

the *in vitro* based effect of etofenprox on FRTL 5 (Fischer rat thyroidal follicular cells). The broadening of the historical control pool that included more data from the rat supplier indicated more variability for thyroid effects than in the initial evaluation. Record 186442 appended to 186442 were not given a review. The argument was being made for a non-genotoxic mechanism for thyroid tumor induction and the use of a MOE. (Green and Gee, 4/03/03).

Report No. MTC 67/85706, 9 October 1985, In the F0 generation, 28 Crl:COBS CD(SD)BR rats per sex group received Ethofenprox (MTI-500) technical (96.3%) in the diet at 0 (SF Laboratory Animal Diet No. 2 + corn oil), 100, 700, and 4900 ppm starting 70 days pre-mating through 2 matings. Twenty-four F1 (F1b) animals per sex were allowed to mate twice. F1b animals were reared to maturity. Water consumption was increased for F1a, F1b, and F2b adults at 4900 ppm relative to controls for various time periods during weeks 5 through 14. F0 and F1b female bodyweights at 4900 ppm were lower (5% to 7%) than controls generally during weeks 4-14 of treatment. Relative (% of bodyweight) F0, F1, and F2b liver, kidney, and thyroid weights were increased at 4900 ppm in both sexes. Necropsy showed an increase in vasculature congestion or hemorrhage in the medulla. Foreskin reteining of the papilla, papillary hypertrophy imlicated changes in the kidneys of F1b animals at 4900 ppm. Cystic collecting enlarged/swollen/misshapen kidneys for F1a, F1b, and F2b adults and weanlings at 4900 ppm.

Histopathology indicated changes in the kidneys of F1b animals at 4900 ppm. Cystic collecting ducts were often associated with focal medullary fibrosis, mineral deposits, and necroses of pyelonephritis was observed in some animals. Cortical scarring and an increased incidence of dilated cortical tubules in females or basophilic tubules in males was also noted. One F0 kidney. In the liver, minimal centrilobular hepatocyte enlargement was recorded in both sexes at 4900 ppm. Thyroid changes were limited to minimal increased height of the follicular epithelium in males (6/23) at 4900 ppm. Although histopathology was not conducted on F0 animals, Report # MTC 64/85422, 28 October 1985, 35 inseminalated Crl COBS CD (SD) BR England, Report # MTC 64/85422, 28 October 1985, (David D. Cozens, et al., Huntingdon Research Centre Ltd., Maturational of the F₁ Generation, (David D. Cozens, et al., Huntingdon Research Centre Ltd.,

**51626-018 186444, "Effect of Ethofenprox (MTI-500) on Pregnancy of the Rat with Rearing to Teratology, Rat" female rats received Ethofenprox (MTI-500) by gavage at 0 (1% methylcellulose), 12.5, 250, and 500 mg/kg/day on gestation days 6 through 17. 21-24 per group were sacrificed on gestation day 20 for teratogenicity evaluation. Remaining females per group were allowed to give birth and rear the offspring through day 21. An F1 generation was selected from those pups to assess the reproductive effects of their previous exposure to Ethofenprox. The untreated reproductive phase continued through weaning of the F2 generation.

Teratogenicity results: Increased salivation was noted for dams at 250 and 500 mg/kg/day. Webrown staining around the mouth and webbrown staining of the analgesic region were increased at 5000 mg/kg/day. The incidence of fetal visceral malformations was slightly higher at 5000 mg/kg/day. One fetus from each of 3 females was affected. 1 fetus with left microphthalmia, another with hydrocephaly and absent innominate artery, and a third with slight microphthalmia and left anophthalmia were noted. The incidence was not statistically significant around the mouth and webbrown staining of the analgesic region at 5000 mg/kg/day.

Developmental NOEL = 5000 mg/kg/day. Reproductive assessment phase: Time to vaginal opening was marginally earlier for F1 females (exposed in utero) relative to controls. In the hole board test, F1 males and females in the 250 and 5000 mg/kg/day groups showed slightly lower mobility than controls. Rearing counts were also lower for males in these groups. F1 females significantly higher than controls. The incidence was not statistically significant around the mouth and webbrown staining of the analgesic region at 5000 mg/kg/day.

Significant on a litter basis. Material NOEL = 250 mg/kg/day (increased webbrown staining right microphthalmia and left anophthalmia were noted. The incidence was not statistically significant on a litter basis. The material NOEL = 250 mg/kg/day (increased webbrown staining of the analgesic region was noted for dams at 250 and 5000 mg/kg/day).

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from all treatment groups also had slightly longer entry times on day 1 and 2 in the passive avoidance test. F2 generation litter results were generally in line with controls. **Acceptable** with no teratogenicity. (Green, Gee, and Leung 4/4/03).

Teratology, Rabbit

51626-017 186451, "Rabbit Developmental Toxicity Study with Etofenprox", (James L. Ivett, Covance Laboratories, Inc., Vienna, VA., Covance study No. 6648-144, 17 January 2001). Twenty mated Hra:(NZW)SPF female rabbits per group were dosed by oral gavage with Etofenprox technical (96.68% purity) at 0 (1% aqueous methylcellulose), 30, 100, and 300 mg/kg/day on gestation days 6 through 28. There were no signs of maternal toxicity in any of the dose groups including clinical signs, bodyweights, bodyweight change, and food consumption. No external findings in any of the fetuses were recorded. No changes in fetal viability or fetal weight were indicated. Maternal NOEL = 300 mg/kg/day. Developmental NOEL was not determined due to incomplete fetal evaluation. **Unacceptable, not upgradeable** (incomplete fetal visceral exam, no skeletal exam). (Green and Gee, 4/4/03).

51626-017 186450, "Dose Range-Finding Developmental Toxicity Study in Rabbits with Etofenprox", (James L. Ivett, Covance Laboratories, Inc., Vienna, VA, Covance Study No. 6648-143, 13 September 2000). Five mated Hra:(NZW)SPF female rabbits per group received etofenprox (96.68% purity) by oral gavage at 0 (1% methylcellulose), 50, 125, 250, and 500 mg/kg/day on gestation days 6 through 28. At 500 mg/kg/day, the incidence of dams with thin appearance and few or no feces was increased. Maternal bodyweight and food consumption were reduced and the number of abortions increased (3/5). Fetal viability and weight were also reduced at 500 mg/kg/day. Maternal and Developmental NOEL = 250 mg/kg/day. **Supplemental information.** (Green and Gee, 4/4/03).

**** 0023; 205046;** "Rabbit Developmental Toxicity Study with Etofenprox"; (B.R. Fisher; Covance Laboratories, Inc., Vienna, VA; Study ID. 6648-146; 9/13/00); Twenty-two mated Hra:(NZW)SPF rabbits/group were dosed orally by gavage with 0 (aqueous 1% methylcellulose), 30, 100 or 300 mg/kg/day of etofenprox technical (lot no. 21088, purity: 96.68%) from gestation day 6 through 28. One doe in the 300 mg/kg group died on study gestation day 26 while aborting. Another doe in the 100 mg/kg group died on gestation day 26. No signs of distress were noted prior to its death. One 300 mg/kg doe was euthanized in moribund condition on gestation day 16. Three does in the 300 mg/kg group and one in the 30 mg/kg group suffered abortions. The mean body weight gain for the 300 mg/kg females was less than that of the control ($p<0.01$). The mean food consumption over the dosing period was reduced as well ($p<0.01$). The mean body weights of the 300 mg/kg fetuses was less than that of the controls ($p<0.01$). Although there was an increased incidence of unossified 5th sternabrae for the 30 and 100 mg/kg fetuses ($p<0.05$), lack of or diminished ossification was not evident for other related skeletal structures. **Possible adverse effect:** Incidence of abortions; **Maternal NOEL:** 100 mg/kg/day (based upon lower mean body weight, food consumption and increased incidence of abortion for the 300 mg/kg females); **Developmental NOEL:** 100 mg/kg/day (based upon lower mean body weights for the 300 mg/kg fetuses); **Study acceptable.** (Moore, 7/8/03)

Gene Mutation

****51626-019 186454,** "Reverse Mutation in *Salmonella typhimurium*", (C.N. Edwards and R. Forster; Life Science Research, Roma Toxicology Centre, Rome, Italy; LSR-RTC Report No. 162001-M-06185, 22 August 1985). *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 were exposed (triplicate plates, 2 trials) to ethofenprox (MTI-500) (96.3% purity), in the presence and absence of S9 activation, at 0 (DMSO), 200, 400, 800, 1600, and 3200 µg/plate for 72 hours. A precipitate formed at 3200 µg/plate. Positive controls were functional. No increase in revertant colonies. **Acceptable.** (Green and Gee, 3/10/03).

****51626-019 186452,** "Gene Mutation in Chinese Hamster V79 Cells", (A. H. Seeberg and R. Forster, Life Science Research, Roma Toxicology Centre, Rome, Italy, LSR-RTC Report No. 162002-M-06985, 22 August 1985). Chinese hamster V79 cells were exposed in triplicate (2 trials)

**51626-019 186453, "MTI-500, Ethofenprox: Assessment of its Mutagenic Potential in Amino-Acid Auxotrophs of *Salmonella typhimurium*", (J. Bootman and K. May, Life Sciences Research Institute, Eyrhrocytes in the Micronucleus Test", (J. Bootman, et al., Life Sciences Research, Eye, Suffolk, England, LSR Report No. 85/MTO016/406, 3 July 1985). 15 (control and high dose) or 5 CD-1 mice per group received a single oral gavage dose of ethofenprox (MTI-500) at 0 (0.5% methylcellulose), 80, 400, and 2000 mg/kg. 5 mice per sex per group were sacrificed 24 hours after treatment for bone marrow evaluation. Further lots of 5 animals per sex from the control and high dose groups were sacrificed 48 and 72 hours post-dosing. Appoximately 2000 erythrocytes were scored per animal. The positive control, chlorambucil, was functional. No increase in micronucleated polychromatic erythrocytes. Acceptable. (Green and Gee, 3/10/03).

**51626-019 186455, "MTI-500, Ethofenprox: Assessment of Clastogenic Activity on Bone Marrow Erythrocytes in the Micronucleus Test", (J. Bootman, et al., Life Sciences Research, Eye, Suffolk, England, LSR Report No. 85/MTO016/406, 3 July 1985). 15 (control and high dose) or 5 CD-1 mice per group received a single oral gavage dose of ethofenprox (MTI-500) at 0 (0.5% methylcellulose), 80, 400, and 2000 mg/kg. 5 mice per sex per group were sacrificed 24 hours after treatment for bone marrow evaluation. Further lots of 5 animals per sex from the control and high dose groups were sacrificed 48 and 72 hours post-dosing. Appoximately 2000 erythrocytes were scored per animal. The positive control, chlorambucil, was functional. No increase in micronucleated polychromatic erythrocytes. Acceptable. (Green and Gee, 3/10/03).

**51626-019 186456, "In Vitro Assessment of the Clastogenic Activity of MTI-500, Ethofenprox, in Cultured Human Peripheral Lymphocytes", (J. Bootman, et al., Life Sciences Research Limited, Eye, Suffolk, England, LSR Report No. 85/MTO021/711, 22 November 1985). Cultures of rat liver S9 activation for 2 and 24 hours were exposed to ethofenprox (MTI-500) (96.3%) at 0 (DMSO), 6.25, 12.5, 25.0, and 50.0 µg/ml in the presence and absence of rat liver S9 activation for 2 and 24 hours. Human blood lymphocytes were exposed to ethofenprox (MTI-500) (96.3%) at 0 (DMSO), 6.25, 12.5, 25.0, 10.0, and 20.0 µg/ml in the absence of S9 activation and 0 (DMSO), 0 (untreated medium), 2.5, 5.0, 15.0, and 30.0 µg/ml in the triplicate cultures (without activation) for 24 hours (activated cultures were washed after 2 hours, then retreated without activation) for a further 22 hours. One hundred metaphases were scored per culture. Mitotic indices were used for evidence of toxicity. No increase in structural chromosomal aberrations. Positive controls were functional. Acceptable. (Green and Gee, 3/10/03).

**51626-019 186458, "MTI-500-a-CO: Assessment of its Ability to Cause Lethal DNA Damage in Strains of *Escherichia Coli*", (J. Bootman and K. May, Life Sciences Research Limited, Eye, Suffolk, England, LSR Report No. 85/MTO022/504, 2 October 1985). Duplicate suspensions (2.5 x 10⁶ cells/ml) of *Escherichia coli* strains WP2, WP67, and CM871 were exposed in the presence and absence of rat liver S9 activation to MTI-500-a-CO (99.6%) at 0 (DMSO), 0 (untreated), 320, 1000, 3200, and 10000 µg/ml for 2 and 18 hours. Bacteria were diluted and plated and the number of colonies per plate scored after 1 day at 37°C. Cell lethality was not increased in repair deficient strains (WP67 and CM871). Positive controls (2-aminoanthracene and mitomycin) were strains (WP67 and CM871). Positive controls (2-aminoanthracene and mitomycin) were functional. Acceptable. (Green and Gee, 3/10/03).

DNA Damage

51626-019 186459, "Unscheduled DNA Synthesis in Human Cells, Cell Line: Hela S3" (A.H. Seeberg and R. Forster, Life Science Research, Rome, Italy, LSR-RTC Report No. 162003-M-05785, 30 July 1985). Human Hela S3 cells were exposed to ethofenprox (MTI-500) (96.3%) in triplicate monolayer cultures at 0 (DMSO), 2.44, 4.88, 9.75, 19.5, and 39.0 $\mu\text{g}/\text{ml}$ in the presence of rat liver S9 mix and at 0 (DMSO), 9.75, 19.5, 39.0, 78.0, and 156 $\mu\text{g}/\text{ml}$ without S9 for 3 hours in the presence of [³H] thymidine in two trials. The highest concentration was based on toxicity and solubility. Replicative DNA synthesis was suppressed in arginine free medium and by hydroxyurea during exposure. DNA was extracted from cell pellets by trichloroacetic acid precipitation followed by hydrolysis in 0.3 M KOH with heating. Label incorporation was determined by LSC and DNA concentration by a colorimetric assay. Results were expressed as DPM/ μg DNA. Positive controls (4-NQO and B(a)P) were functional. No increase in unscheduled DNA synthesis. **Acceptable. (Green and Gee, 4/9/03).

STUDIES ON METABOLITES

005; 186415; "MTI-500 α -Co: Acute Toxicity Study in the Rat" (Cummins, H.A. and Gardner, J.R., Life Science Research Limited, Eye, Suffolk, England, Laboratory Project ID 85/MT0018/474, 8/2/85). MTI-500 α -Co (Batch OFU-1021, purity = 99.6%), suspended in maize oil, was administered as a single gavage dose to 5 CD rats (remote Sprague-Dawley origin) per sex at a dose level of 5000 mg/kg. No mortalities occurred. Decreased motor activity was observed in all animals 2 hours after dosing clearing in all animals 4 hours after dosing. Necropsy revealed dark submandibular salivary glands in 2 males and large cervical lymph nodes in 1 male. LD₅₀ (M/F) > 5000 mg/kg. NOEL not determined. **Supplemental study** (the test material used in the study was not the active ingredient in review) (Corlett, 11/6/02)

005; 186416; "Ethofenprox (MTI-500) Acute Limit Test of Toxicity to Dogs Following a Single Oral Administration" (Harling, R.J. et al., Department of Dog Toxicology, Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, England, Laboratory Project ID MTC 101/851185, 10/24/85). Ethofenprox (MTI-500) (Batch ST103, purity = 96.3%) was inserted into gelatine capsules and 1 pure-bred beagle dog per sex was dosed once with 5000 mg/kg. No mortalities occurred. Semi-soft green feces approximately 2 hours after dosing and semi-soft feces of normal color on Days 2 and 4 were observed in the male; no clinical signs were observed in the female. Small weight loss was observed in the female for 3 days following dosing and at the end of the 14 day observation period. Necropsy revealed no treatment-related abnormalities. Bone marrow smears taken from each animal prior to terminal sacrifice were found to be normal in cellularity, morphology, and cell distribution. LD₅₀ (M/F) > 5000 mg/kg. NOEL not determined. **Supplemental study** (only 1 animal per sex per dose group used) (Corlett, 11/6/02)

CONCLUSIONS: Do data support registration?

Toxicity data were submitted to support a Section 3 registration request for Etufenprox Technical for manufacturing use only.

The acute oral, dermal and inhalation toxicity and primary dermal and ocular irritation studies are acceptable. MTI-500 is not a potential dermal sensitizer as indicated by the dermal sensitization study. Acceptable acute studies were submitted for a formulated product, Zoecon F254-87-1 Aerosol.

Subchronic oral feeding studies with rodents, 28-day repeated dose dermal toxicity study and 90-day inhalation study in rats are acceptable.

Animal metabolism studies in dogs and rats were submitted. Collectively, the data fulfills the current requirements for an acceptable metabolism study.

Chronic feeding studies in rodents (rats and mice) and dogs are acceptable.

RECOMMENDATIONS: What type of registration action is being considered? In the case of ongoing registration, register or do not register? What other specific studies or data are requested?

Acceptable studies were submitted to satisfy the current data requirements for gene mutation, chromosomal effects and DNA effects.

The rat and rabbit developmental and reproduction studies are acceptable.

Submitted as a Section 3 registration request for manufacturing use only. The data reviewed are adequate for a complete toxicological evaluation. The product label adequately identifies the acute toxicity hazards indicated by the data reviewed. Registration is recommended. In accordance with DPR policy, the risk assessment on the active ingredient will be conducted after registration as prioritized by the SB950 Adverse Effects Advisory Panel (see memorandum of 8/22/96).

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Thomas Moore, Ph.D.

Date
12/8/93

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