CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
Etofenprox

Chemical Code # 002292, **Tolerance** # 51626

Original: 11 April 2003
Revised: 18 September 2003
Revised: 5 December 2003

I. DATA GAP STATUS

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

Toxicology one-liners are attached.

All record numbers through 208112 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study in review.
File name: T030411, prepared by Green and Gee.
Revised file name: T031205, prepared by Moore

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

****51626-011, 012 186428, 186439**, "Ethofenprox (MTI-500) Potential Tumorigenic and Toxic Effects in Prolonged Dietary Administration to Rats (Final Report)", (Owen P. Green, *et al*., Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, England, Report # MTC 59/85581, 24 January 1986). 70 CD rats per sex per group of Sprague-Dawley origin received ethofenprox (MTI 500) technical (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 main and satellite group animals 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 equivalents at 30, 100, 700, and 4900 ppm during the treatment period were 1.1 and 1.4; 3.7 and 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 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 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, RAT

See Combined Rat, above.

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 centribolular 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, RAT

See Combined Rat, above.

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).

REPRODUCTION, 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 Crl: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-mating through 2 matings. Twenty-four F1 (F1b) animals per sex per group were allowed to mate twice. F2 (F2b) 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 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 noted and were often associated with focal medullary fibrosis, mineral deposits, and vascular congestion or hemorrhage in the medulla. Foreshortening of the papilla, papillary necrosis or 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 700 ppm 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 F0 reproductive organs/tissues, a thorough exam was done on the F1b adults. Parental NOEL = 700 ppm (cystic collecting in kidneys at 4900 ppm). Reproductive NOEL = 4900 ppm. Pup NOEL = 700 ppm (lower pup weight and pup loss (days 12 to 21) at 4900 ppm). No adverse effects. Acceptable. (Green and Gee, 4/9/03).

TERATOLOGY, RAT

51626-016 186444, "Effect of Ethofenprox (MTI-500) on Pregnancy of the Rat with Rearing to Maturation of the F_1 Generation",** (David D. Cozens, *et al*., Huntingdon Research Centre Ltd., England, Report # MTC 64/85422, 28 October 1985). 35 inseminated Crl COBS CD (SD) BR female rats received Ethofenprox (MTI-500) technical (96.3% purity) by gavage at 0 (1% methylcellulose), 12.5, 250, 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 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 *in utero* 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. 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 anaphthalmia 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).

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

**51626-019 186453, "MTI-500 α-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/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-500α-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. Acceptable. (Green and Gee, 4/8/03).

CHROMOSOME EFFECTS

**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/MT0016/406, 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* 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/MT0017/430, 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 presence and absence of rat liver 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 186457, "*In Vitro* Assessment of the Clastogenic Activity of MTI-500 α-CO in Cultured Human Peripheral Lymphocytes", (J. Bootman *et al*., Life Science Research Limited, Eye, Suffolk, England, LSR Report No. 85/MT0021/711, 22 November 1985). Cultures of male human blood lymphocytes in whole blood were exposed to MTI-500 α-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 at 0 (DMSO), 0 (untreated medium), 37.5, 75.0, 150, and 300 µg/ml in the presence of rat liver S9. Cultures were treated 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).

DNA DAMAGE

**51626-019 186458, "MTI-500 α-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/MT0022/504, 2 October 1985). Duplicate suspensions (2-5 x 10^8 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 α-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 functional. 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 [^{3}H] 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).

NEUROTOXICITY

Not required at this time.

METABOLISM, RAT

**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). Single (30 and 180 mg/kg) and multiple (30 mg/kg/day for 7 or 14 consecutive days) doses of ^{14}C-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 ^{14}C-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 ^{14}C-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 ^{14}C-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 ^{14}C-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 ^{14}C-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).

**51626-020 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 µg/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 µg/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 µg/cm^2 after 96 hours. Acceptable. (Green and Gee, 3/13/03).

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, 12/11/02)

(Inhalation)

51626-009, -0025; 186426, 208112; "Ethofenprox (MTI-500) 90-Day Inhalation Study in Rats" (Coombs, 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% 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 (mean analytical concentration) of 0 (air control), 0 (acetone only, at a concentration equal to the acetone concentration at the high dose level), 0.042, 0.21, 1.01 mg/l (with an average of 90.1% to 90.9% of the test material < 5.5 µm 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. Macroscopic examination revealed enlarged adrenals 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 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 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 weights together a minimal enlargement of centrilobular hepatocytes and a minimally increased number of microfollicles and minimally increased height of follicular epithelium in the 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 data and calculations used to determine the mean analytical concentrations of the test material, **Study acceptable**. (Corlett, 12/3/02, revised, Moore, 12/5/03)

METABOLISM, DOG

**51626-020 186460, "The Metabolism of ^{14}C-Ethofenprox in Dogs", (D. R. Hawkins, *et al*., Department of Chemical Metabolism and Radiosynthesis, Huntingdon Research Centre, Huntingdon, 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. Radioactivity 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 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-de-ethylation 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).

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)