CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Flutriafol

Chemical Code # 5971, **Tolerance #** 53051
SB 950 # NA

Original: 2/9/09
Revised: 12/16/09

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect indicated
Chronic toxicity, dog:	Data gap, no adverse effect indicated*
Oncogenicity, rat:	No data gap, no adverse effect indicated
Oncogenicity, mouse:	No data gap, possible adverse effect
Reproduction, rat:	No data gap, no adverse effect indicated
Teratology, rat:	No data gap, possible adverse effect
Teratology, rabbit:	No data gap, no adverse effect indicated
Gene mutation:	No data gap, no adverse effect indicated
Chromosome effects:	No data gap, no adverse effect indicated
DNA damage:	No data gap, no adverse effect indicated
Neurotoxicity:	No data gap, possible adverse effect

Toxicology one-liners are attached.

All record numbers through # 248742 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T091216
Revised by T. Moore, 12/16/09

* Note: Dog Subchronic Oral Toxicity Study (rec. no. 236743) is sufficient to fulfill this data requirement.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

COMBINED, RAT

** 0026, 0038; 236768, 248738; "Flutriafol: 2 Year Feeding Study in Rats" (Pigott, G.H., Imperial Chemical Industries PLC, Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Laboratory Report No. CTL/P/1220, CTL Study No. PR0542, 05/22/86). 870.4300. Flutriafol (batch P10, purity = 93%) was admixed to the diet and fed to 64 Alpk:AP rats per sex per dose at dose levels of 0, 20, 200, or 2000 ppm (0, 1, 10, and 100 mg/kg/day, respectively, values calculated by the reviewer) for 104 weeks. 52 animals per sex per dose were used in the main group and 12 animals per sex per dose were used in the satellite group. In the satellite group, 12 animals from each sex were sacrificed at week 52. Submitted survival rate data- males: 0.476, 0.470, 0.512, 0.465, respectively; females: 0.365, 0.444, 0.481, 0.560, respectively. Animals at 2000 ppm were reported appearing thin with a decreased number exhibiting distended abdomen. A treatment-related decrease in mean body weight gain was observed in both sexes at 2000 ppm throughout the study. A treatment-related decrease in mean food consumption was observed in both sexes at 2000 ppm during the first year of the study, persisting in females during second year but not the males. Treatment-related decreases in mean hemoglobin, mean hematocrit, mean cell volume, and mean cell hemoglobin levels in both sexes were observed at 2000 ppm throughout the study. A treatment-related increase in mean serum total iron binding capacity in females at 2000 ppm at week 104 was observed. Treatment-related increases in mean protein and cholesterol levels in females at 2000 ppm and a treatment-related decrease in the mean triglyceride level in males at 2000 ppm were observed throughout the study. A treatment-related increase in liver weight adjusted to body weight (determined by analysis of covariance) was observed in interim sacrifice males and females (at 2000 ppm) and in terminal sacrifice group males (at 200 and 2000 ppm) and females (at 2000 ppm). Microscopic examination on animals sacrificed at 52 weeks revealed treatment-related centrilobular hypertrophy in both sexes at 2000 ppm but not to a significant degree in animals sacrificed after 52 weeks. Microscopic examination on animals sacrificed after the 52-week interim sacrifice revealed a treatment-related increase in fatty change of the liver in both sexes at 200 and 2000 ppm, treatment-related hemosiderin accumulation in Kupffer cells of the liver in females at 2000 ppm, and a treatment-related increased hemosiderin accumulation in the spleen in both sexes at 2000 ppm. Histopathological examination revealed no treatment-related neoplasms. **No adverse effects.** NOEL (M/F) = 1 mg/kg/day (20 ppm) based on an increase in fatty change of the liver. Study was previously unacceptable but possibly upgradable with the submission of mortality, observations, hematology values, serum chemistry values, urinalysis values, results of the ophthalmological examinations, necropsy findings, and histopathology findings of the individual test animals used; study data submitted in rec. no. 248738 was sufficient to fulfill the study requirements. **Study acceptable.** (Corlett and Leung, 08/06/08, revised, Moore, 11/16/09)

CHRONIC TOXICITY, RAT

See Combined, Rat, above.

CHRONIC TOXICITY, DOG

0025, 236767; "Flutriafol: 1 Year Oral Dosing Study in Dogs" (Stonard, M.D., Imperial Chemical Industries PLC, Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Laboratory Report No. CTL/P/2019, CTL Study No. PD0667, 05/18/88). 870.4100. Flutriafol (batch number P10, purity = 93.0%) was administered by gelatin capsules to 4 beagle dogs per sex per dose at dose levels of 0 (empty gelatin capsules), 1, 5, and 20 mg/kg/day daily for 52 weeks. One female at 20 mg/kg/day was sacrificed during week 16 due to poor clinical condition; no other mortalities occurred. Other than the one female at 20 mg/kg/day that was sacrificed

during week 16 due to poor clinical condition, no treatment-related clinical signs were observed. A treatment-related decrease in mean body weight gain was observed in both sexes at 20 mg/kg/day during the initial weeks of the study persisting in females throughout the study. A treatment-related decrease in mean hemoglobin and hematocrit levels were observed in males at 20 mg/kg/day. A treatment-related increase in mean plasma alkaline phosphatase levels in both sexes at 20 mg/kg/day was observed at 4, 26, and 52 weeks. A treatment-related increase in liver weight was observed in both sexes at 20 mg/kg/day. Microscopic examination revealed treatment-related increased hemosiderin pigmentation in the liver and spleen and treatment-related increased cortical vacuolation in the zona fasciculata of the adrenal glands in both sexes at 20 mg/kg/day. **No adverse effects.** NOEL (M/F) = 5 mg/kg/day based on increased hemosiderin pigmentation in the liver and spleen and increased cortical vacuolation in the zona fasciculata of the adrenal glands. **Unacceptable but possibly upgradable** with the submission of required urinalysis data. (Corlett and Leung, 07/24/08)

ONCOGENICITY, RAT

See Combined, Rat, above.

ONCOGENICITY, MOUSE

**** 0027, 236769;** "Flutriafol: 2 Year Feeding Study in Mice" (Hext, P.M., Imperial Chemical Industries PLC, Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Laboratory Report No. CTL/P/1930, CTL Study No. PM0637, 06/03/88). 870.4300. Flutriafol (batch P10 (reference number Y01433/003), purity = 93.0%) was admixed to the diet and fed to 50 C57BL/10JfCD-1/Alpk (C57BL/10J) mice per sex per dose at dose levels of 0, 0, 10, 50, or 200 ppm (0, 1.5, 7.5, and 30. mg/kg/day, respectively, values calculated by the reviewer) for 2 years. Survival rate data- males: 0.540, 0.560, 0.574, 0.640, 0.500, respectively; females: 0.620, 0.460, 0.500, 0.540, 0.480, respectively. Treatment-related discharge from eye and thickened eyelids were observed in the males at 200 ppm. A treatment-related decrease in mean body weight was observed in both sexes at 200 ppm throughout the study. Treatment-related increases in mean white blood cell and platelet counts were observed at 200 ppm in males at the termination of the study. A treatment-related increase in liver weight adjusted to body weight (determined by analysis of covariance) was observed in both sexes at 200 ppm. Microscopic examination on animals sacrificed at the termination of study revealed treatment-related centrilobular hypertrophy\pard plain in the liver in males at 200 ppm and treatment-related increase in fatty change of the liver in both sexes at 50 and 200 ppm. There was an increase in neoplasm (generalized composite lymphomas) in high dose female mice which died before terminal sacrifice. However, when the incidences of neoplasm (tumors) from both unscheduled and scheduled sacrifice were combined, there was no statistical significance. NOEL (M/F) = 1.5 mg/kg/day (10 ppm) (calculated by the reviewer) based on an increase in fatty change of the liver. **Acceptable** as an oncogenicity study. (Corlett and Leung, 10/17/08)

REPRODUCTION, RAT

** 0024, 236764; "Flutriafol: Two Generation Reproduction Study in the Rat" (Doe, J.E., Imperial Chemical Industries PLC, Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Laboratory Report No. CTL/P/1368, CTL Study No. RR0229, 04/17/86). 870.3800. 15 males and 30 female Alpk:AP (Wistar derived) rats were administered Flutriafol (Batch Number 10, purity = 93.0%) in the diet at dose levels of 0 (diet only), 60, 240, and 1000 ppm for both the F_0 and F_1 generations. The premating period was 12 weeks from the start of the study for the F_0 parents and 11 weeks from the selection for the F_1 generation parents. Females from each generation were mated with males from the same dose group after the premating period. The litters were weaned at day 29 *post partum*. No apparent treatment-related mortalities occurred in the parents. No treatment-related clinical signs were reported in the parents. Treatment-related decreases in mean body weight gain and mean food consumption were observed in both sexes in the premating F_0 parents at 1000 ppm and in the female premating F_1 parents at 1000 ppm. A

treatment-related decrease in mean pregnancy body weight gain was observed in both F_0 and F_1 parents (litter B). A treatment-related increase in liver weight adjusted to body weight (determined by analysis of covariance) was observed in both sexes in the F_0 and F_1 parents at 1000 ppm. Gross necropsy revealed no treatment-related findings in the F_0 and F_1 parents. Microscopic examination of the F_0 and F_1 parents (males and females) and of pups in the F_{1B} and F_{1B} litters revealed treatment-related fatty change in the liver. **No adverse effects.** Maternal NOEL = 240 ppm based on decreased weight gain, an increase in liver weight (adjusted for body weight), and fatty change in liver. Offspring NOEL= 240 ppm based on fatty change in the liver. **Acceptable.** (Corlett and Leung, 09/23/08)

TERATOLOGY, RAT

0023, 236762; "PP450 (Flutriafol): Tertatogenicity Study in the Rat" (Killeck, M.E. et al., Imperial Chemical Industries PLC, Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Laboratory Report No. CTL/P/756, CTL Study No. RR0211, 10/27/82). 870.3700. PP450 (Flutriafol) (Batch Number P10, purity = 93%) was administered as a single daily dose by gavage to 24 mated female Alderley Park Wistar-derived rats per dose at dose levels 0 (corn oil), 10, 50, or 125 mg/kg/day from gestation day 6 through gestation day 15 (inclusive). No maternal deaths were observed. Treatment-related staining of the genital/ventral fur was observed at 125 mg/kg/day. Treatment-related decreases in mean body weight gain and food consumption were observed at 125 mg/kg/day. Macroscopic examination of the dams revealed no treatment-related changes. A treatment-related increase in the number of early and late intra-uterine deaths was observed at 125 mg/kg/day along with treatment-related decreases in mean live fetal weight, mean total litter weight, and mean gravid uterus weight at this dose level. A treatment-related increase in the number of fetuses with cervical ribs (unilateral or bilateral) was observed at 50 and 125 mg/kg/day. **No adverse effects indicated. Reported Maternal NOEL** = 50 mg/kg/day (based on decreased weight gain and food consumption), **Developmental NOEL** not determined due to missing individual fetal data. **Unacceptable but possibly upgradable** with the submission of data recorded on the individual dams and individual fetuses (including body weights) and a clarification of the apparent discrepancy between the text on page 15 and the data in the Table 7 (on page 31) concerning the number of fetuses examined internally for macroscopic visceral abnormalities and the number of fetuses examined for skeletal defects. (Corlett and Leung, 08/26/08)

**** 53051-0039; 248739**; "Flutriafol Technical: Prenatal Developmental Toxicity Study in Han Wistar Rats"; (R. Gerspach; RCC Ltd., 4414 Fullinsdorf, Switzerland; Study No. A10541; 1/22/08); Twenty two mated female Hans Wistar rats/group were dosed orally by gavage with 0 (vehicle: corn oil), 2, 5, 10 or 75 mg/kg/day of Flutriafol Technical (batch no. UPL Bx 1 (2001); purity: 95.1%) from day 6 through day 20 of gestation. No maternal deaths resulted from the treatment. The mean body weight gain of the 75 mg/kg dams during 6 to 9 days of gestation was slightly less than that of the control group. The mean food consumption of the high dose group was less than that of the control group through out the study. The incidence of late resorptions was increased for the dams in the 75 mg/kg group. Malformations of the hyoid bone were noted for the fetuses in the 75 mg/kg group. In addition, increased incidences of various skeletal variations were noted for the fetuses in the 75 mg/kg group. **Possible adverse effect:** increased incidences of late resorptions and malformations of the hyoid bone. **Maternal NOEL:** 10 mg/kg/day (based upon the lower body weight gain and food consumption of the 75 mg/kg dams); **Developmental NOEL:** 10 mg/kg/day (based upon the increased incidence of fetal resorptions and malformations in the 75 mg/kg fetuses); **Study acceptable.** (Moore, 11/17/09)

53051-0039; 248739; "Flutriafol Technical: Dose Range-Finding Prenatal Developmental Toxicity Study in the Han Wistar Rat"; (R. Gerspach; RCC Ltd., 4414 Fullinsdorf, Switzerland; Study No. A10530; 1/22/08, amended, 6/6/05); Five mated Hans Wistar female rats/group were dosed orally by gavage with 0 (vehicle: corn oil), 5, 10, 50 or 150 mg/kg/day of Flutriafol Technical

(batch no. UPL Bx 1 (2001); purity: 95.1%) from day 6 through day 20 of gestation. One female in the 150 mg/kg group was euthanized *in extremis* on day 12. Clinical signs of discomfort and hunched posture were noted for the dams in the 50 and 150 mg/kg groups. Food consumption was less for the dams in these two groups. Body weight gain was reduced in a dose-related manner for all of the treatment groups. Two dams in the 150 mg/kg group suffered total resorptions. The mean fetal body weight of the 150 mg/kg group was less than that of the control group. One fetus in the 150 mg/kg group suffered a domed head, ablepharia, micrognathia, and suspected cleft palate. Based on these results, treatment levels of 0, 2, 5, 10, and 75 mg/kg/day were selected as the doses for the guideline study. **Study supplemental.** (Moore, 11/16/09)

TERATOLOGY, RABBIT

** 0023, 236763; "PP450 (Flutriafol): Tertatogenicity Study in the Rabbit" (Kilmartin, M and Godley, M.J., Imperial Chemical Industries PLC, Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Laboratory Report No. CTL/P/747, CTL Study No. RR0214, 10/20/82). 870.3700. PP450 (Flutriafol) (Batch Number P10, purity = 93%) was administered via a capsule to 18 (19 at 15 mg/kg/day) mated female Dutch rabbits per dose at dose levels 0 (empty gelatin capsule), 2.5, 7.5, or 15 mg/kg/day from gestation day 6 through gestation day 18 (inclusive). The number of mortalities (or animals sacrificed) per dose level occurred as follows: 1, 0, 2 (including one that partially aborted litter), and 2, respectively. A decrease in body weight gain in the does was observed during dosing. Macroscopic examination of the does revealed no treatment-related changes. A treatment-related increase in the number of early and late intra-uterine deaths was observed at 15 mg/kg/day. No treatment-related fetal defects were observed. **No adverse effects**. **Maternal NOEL** = 7.5 mg/kg/day (based on decreased number of live fetuses per animal), **Developmental NOEL** = 15 mg/kg/day (based on no effects at the highest dose tested). **Acceptable.** (Corlett and Leung, 09/08/08)

GENE MUTATION

** 0028, 236771; "PP450- An Evaluation in the *Salmonella*/Microsome Mutagenicity Assay" (Longstaff, E., Imperial Chemical Industries PLC, Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Laboratory Report No. CTL/P/730, CTL Study Nos YV0603, YV0625, 02/08/88). 870.5100. Triplicate cultures of *Salmonella typhimurium* cell lines TA1535, TA1537, TA1538, TA98, and TA100 were exposed (direct plate incorporation method) to PP450 (Batch ref P10 (CTL reference number Y01433/003/016), purity = 93%), in the presence and absence of S9 rat liver fraction, at 0 (DMSO), 8.0, 40, 200, 1000, 2500, and 5000 µg/plate and incubated at 37°C for 66-70 hours in the dark. Positive controls were functional. There was no treatment-related increase in mutation frequency. **No adverse effects indicated. Acceptable**. (Corlett and Leung, 10/27/08)

0028, 236774; "PP450 (Flutriafol)- Assessment of Mutagenic Potential in the Mouse Lymphoma Assay" (McGregor, D.B., Inveresk Research International, Musselburgh, Scotland, Laboratory Study No. 730420, Laboratory Report No. 2893, 05/15/86). 870.5300. Triplicate cultures of the $TK^{+/-}$ mouse lymphoma L5178Y cell line were treated with PP450 (Ref. No. Y01433/003/017, no purity data provided), in the presence and absence of S-9 rat liver fraction, for 3 hours at concentrations ranging from 33 to 1000 µg/ml in the first assay, from 150 to 750 µg/ml in the second assay, and from 50 to 650 µg/ml in the third assay. Positive controls were functional. The presented data demonstrated a significant increase (compared the solvent control) in the number of TFT^{+} colonies at concentrations of 100, 333, and 1000 µg/ml (Assay 1) and at concentrations of 600 and 750 µg/ml (Assay 2) (both in the presence of S-9 activation) and a significant increase mutation frequency at concentrations 500 and 650 µg/ml, also in the presence of S-9 activation (Assay 3). However, significantly decreased cell viability was also observed at the same concentrations in Assay 2 and Assay 3 listed above. Therefore, it cannot be determined from the data presented whether or not the test material is mutagenic. **No adverse**

effects indicated. Unacceptable but possibly upgradable with the submission of information concerning the purity of the test material. (Corlett and Leung, 11/05/08)

** 53051-0040; 248742; "Cell Mutation Assay at the Thymidine Kinase Locus (tk +/-) in Mouse Lymphoma L5178Y Cells with Flutriafol Technical"; (H-E. Wollny; Mouse lymphoma L5178Y cells were treated with Flutriafol Technical (batch no. BX-No-01 (subsample of UPL Bx 1 (2001)); purity: 95.1%) at concentrations ranging from 25.0 to 600.0 ug/ml under conditions of both non-activation under conditions of activation for 4 hours at 37° C in the first experiment. In the second experiment, the cells were exposed to concentrations ranging from 12.5 to 400.0 ug/ml for 24 hours w/o activation. In the 3rd experiment, cells were exposed to concentrations ranging from 200.0 to 400.0 ug/ml for 4 hours under conditions of activation. Duplicate cultures/treatment level were included in the study. A phenobarbital/beta-naphthoflavone-induced rat liver S9 fraction was used to metabolize the test material. Cell survival and viability and mutation frequency for each treatment level were determined and compared to those of the solvent and/or negative control. There was no dose-related increase in mutation frequency under conditions of either non-activation or activation. Positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 11/24/09)

CHROMOSOME EFFECTS

** 53051-0028, -0040; 236775, 248741; "Flutriafol: An Evaluation in the *In Vitro* Cytogenetic Assay in Human Lymphocytes" (Howard, C.A., Imperial Chemical Industries PLC, Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Laboratory Study No. SV0343, Laboratory Report No. CTL/P/2569, 06/19/89). 870.5375. Duplicate cultures of human lymphocytes (from 2 donors) were treated with Flutriafol (technical material) (CTL reference number Y01433/047/001, purity = 92.8% w/w) in the presence and absence of S-9 rat liver fraction, for approximately 2 hours 15 minutes to 3 hours 35 minutes at concentrations of 0, 25, 125, and 250 µg/ml approximately 44 hours after cell culture initiation. Dividing lymphocytes were arrested at metaphase by treatment with colchicine at 70 hours. Calculated mean % abnormal cells in the replicates indicated no treatment- related chromosomal aberrations. However, the observations of individual cells at metaphase were not presented in the test report. Positive controls were functional. **No adverse effects indicated.** Study was previously unacceptable, but possibly upgradable with the submission of a listing of the individual chromosomal aberrations observed in individual cells at metaphase; submitted information in record no. 248741 was sufficient to upgrade the study; **Study acceptable.** (Corlett and Leung, 11/14/08, revised, Moore, 11/19/09)

** 0028, 236776; "PP450 (Flutriafol)- A Cytogenetic Study in the Rat" (Styles, J.A., Imperial Chemical Industries PLC, Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Laboratory Report No. CTL/P/725, 02/09/82). 870.5385. PP450 (Batch, CTL Test Substance Number: Y01433/003/006, purity = 93%) was prepared in corn oil and administered by gavage to 3 groups of 8 Alderley Park rats per sex per dose at dose levels of 15, 70 and 150 mg/kg. The first group was dosed once and terminated after 6 hours, the second group was dosed once and terminated after 24 hours, the third group was dosed daily for 5 days and terminated 6 hours after the final dose. Each group also consisted of 12 animals dosed with corn oil only (negative control group) and 12 animals dosed with the positive control substance cyclophosphamide. Bone marrow cells from the femur were examined for chromosomal aberrations . No treatment-related increase in the incidence of chromosomal aberrations was noted. The positive control was functional. **No adverse effects indicated. Acceptable.** (Corlett and Leung, 11/24/08)

** 0028, 236777; "Flutriafol: An Evaluation in the Mouse Micronucleus Test" (Richardson, C.R., Imperial Chemical Industries PLC, Central Toxicology Laboratory, Alderley Park, Macclesfield,

Cheshire, UK, Laboratory Report No. CTL/P/1470, Laboratory Study No. SM0216, 04/02/86). 870.5395. Flutriafol (CTL reference number Y01433/003/009, purity = 93%) was prepared in corn oil and administered by gavage to 15 C57BL/6J/Alpk mice per sex per dose at dose levels of 0 (corn oil), 93.8 and 150 mg/kg with 5 per sex per dose sacrificed 24 hours after treatment, 5 sacrificed 48 hours after treatment, and 5 sacrificed 72 hours after treatment. The same number of animals were treated with the positive control material cyclophosphamide at a dose level of 65 mg/kg. Bone marrow samples from the femur were examined and the mean number of polychromatic erythrocytes (PCE) with micronuclei per 1000 PCEs/animal was determined. No treatment-related increase in the number of micronucleated PCE's was noted. The positive control was functional. **No adverse effects indicated. Acceptable.** (Corlett and Leung, 12/01/08)

** 0028, 236778; "PP450: Dominant Lethal Study in the Mouse" (Longstaff, E., Imperial Chemical Industries PLC, Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Laboratory Report No. CTL/P/746, Laboratory Study No. RM0206, 09/28/82). 870.5450. PP450 (Batch P10, approximate purity of 93%), suspended in corn oil, was administered by gavage to 20 male CD-1 mice per dose at dose levels of 0 (corn oil), 25, 50, and 100 mg/kg/day for 5 consecutive days. Each of the 15 healthiest males per dose group was selected to breed with 2 females for 7 consecutive nights. On the 7th day after mating, each male was removed from the cage and placed in a clean cage. This procedure was repeated each week until 8 test matings had been conducted. Females were sacrificed 16 days after being paired with the males and their uteri were examined for numbers of live implantations, early deaths, and late deaths. The same number of animals were treated with positive control materials ethyl methanesulphonate (EMS) at a dose level of 150 mg/kg/day and cyclophosphamide (CTX) at a dose level of 200 mg/kg (a single intraperitoneal injection on day 5). There were no treatment-related effects on live implantations, early deaths, or late deaths. The positive controls were functional. **No adverse effects indicated. Acceptable.** (Corlett and Leung, 12/08/08)

** 53051-0040; 248740; "Chromosome Aberration Test in Human Lymphocytes with Flutriafol Technical"; (S.Kunz; RCC, Cytotest Cell Research GmbH (RCC-CCR), D-64380 Rossdorf, Germany; Study No. 1031002; 2/28/07); Primary human lymphocyte cultures in whole blood (stimulated with PHA for 50 to 80 hours), procured from healthy female volunteers, were treated with Flutriafol Technical (batch no. BX-No-01 (subsample of UPL Bx 1 (2001)); purity: 95.1%). In trial no. 1, the cells were exposed to concentrations of the test material ranging from 17.2 to 2650 ug/ml with and w/o activation for 4 hours and incubated for an additional 18 hours. In addition, cells were exposed to same range of concentrations for 22 hours w/o activation. In a confirmatory assay, the cells were exposed to a range of concentrations from 25.0 to 1750 ug/ml for 4 hours and incubated for an additional 18 hours. In trial no. 2, the non-activated samples were exposed to concentrations of the test material ranging from 9.7 to 489.8 ug/ml for 46 hours. The activated preparations were exposed for 4 hours to concentrations of the test material ranging from 91.4 to 2650 ug/ml followed by an additional 42 hours of incubation A phenobarbital/beta-naphthoflavone-induced rat liver S9 fraction was used to metabolize the test material. Two hundred metaphases/treatment level were examined for structural abnormalities. No treatment-related increase in chromosomal aberrations was evident under conditions of nonactivation or activation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 11/18/09)

DNA DAMAGE

** 0028, 236780; "Flutriafol: Assessment for the Induction of Unscheduled DNA Synthesis in Rat Hepatocytes *In Vivo*" (Trueman, R.W., Imperial Chemical Industries PLC, Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Laboratory Report No. CTL/P/1841, 06/16/87). 844. Flutriafol (P10, CTL reference number: Y01433/003/022, purity = 93.0%) was prepared in corn oil and administered by gavage to 2 groups of 1-3 Alderley Park

(Alpk:AP) rats per dose at dose levels of 0 (corn oil only), 250, 500, and 1000 mg/kg of which 1 group was sacrificed 4 hours after dosing and the other group was sacrificed 12 hours after dosing (a second experiment was conducted in a similar manner to confirm the results of the first). A positive control group (using 6BT) was included in each experiment. After sacrifice, suspensions of hepatocytes from each animal were prepared and plated out into 3 petri dishes that contained a 25 mm round coverslip. The cells were then treated with ^{3}H- thymidine for 4 hours and chased overnight. Autoradiography was then conducted on the cells. At least 25 but normally 50 cells (morphologically unaltered) per slide and a total of 100 cells per animal were examined where possible. These observations indicated no treatment-related unscheduled DNA synthesis in the treated hepatocytes at either time point. The positive control was functional. **No adverse effects indicated. Acceptable.** (Corlett and Leung, 12/12/08)

NEUROTOXICITY

Rat Dose Range-Finding for Acute Neurotoxicity Study

0031; 236786; "Oral (Diet) Dosage Range-Finding Subchronic Neurotoxicity Study of Flutriafol in Rats" (Barnett, J.F., Charles River Laboratories Preclinical Services, Horsham, PA, Laboratory Project ID TQC00007, 06/30/06). Flutriafol (lot number UPL Bx 1 (2001), purity = 95.1%) was admixed to the diet (using acetone) and fed to 5 Crl:CD(SD) rats per sex per dose at dose levels of 0, 1000, 2000, or 4000 ppm (0, 86.8, 177.6, and 323.7 mg/kg/day, respectively for males and 0, 84.4, 162.5, and 301.4 mg/kg/day, respectively for females) for 29 days. No animals died during the study. Treatment-related dehydration was observed 4/5 males at 4000 mg/kg. A treatment-related decrease in mean body weight between days 1 and 8 was observed in both sexes at 4000 ppm; partial recovery of this body weight decrease was observed in females but not males toward the end of the study. A treatment-related decrease in mean food consumption was observed in both sexes at 4000 ppm between days 1 and 8; this decrease in food consumption was not observed between days 15 and 29. A central nervous system screen that included evaluations of posture, gait abnormality, alertness, and other unusual behavior in an open field arena revealed no abnormalities. Necropsy revealed no abnormalities. **No adverse effects.** NOEL (M) = 177.6 mg/kg/day (2000 ppm) and NOEL (F) = 162.5 mg/kg/day (2000 ppm) based on a decrease in body weights and clinical signs (dehydration in males). **Supplemental study** because only 5 animals were used per dose level, the animals were dosed for only 29 days, and no neuropathology was performed on the test animals. (Corlett, 06/18/08)

0031; 236787; "Acute Oral (Gavage) Dosage Range-Finding Study of Flutriafol in Rats" (Barnett, J.F., Charles River Laboratories Preclinical Services, Horsham, PA, Laboratory Project ID TQC00005, 06/26/06). Flutriafol (lot number UPL Bx 1 (2001), purity = 95.1%), prepared in corn oil, was administered in a single dose by gavage to 5 Crl:CD(SD) rats per sex per dose at dose levels of 0 (vehicle only), 125, 250, 500, or 1000 mg/kg. The animals were then observed for 3 days. Mortalities (animals either found dead or sacrificed due to moribund condition)- males: 0/5, 0/5, 0/5, 1/5, 4/5, respectively; females: 0/5, 0/5, 0/5, 0/5, 5/5, respectively. Ataxia was observed 1/5 males at 500 mg/kg and in 3/5 males and 2/5 females at 1000 mg/kg within 8 hours after dosing. Also, ptosis, bradypnea, cold to touch, dehydration, urine-stained abdominal fur, decreased motor activity, and lost or impaired righting reflex were observed in both sexes at 1000 mg/kg. A decrease in mean body weight gain and a decrease in mean food consumption were observed in males at doses beginning at 125 mg/kg and in females at doses beginning at 250 mg/kg between days 1 and 2. No clinical signs were observed in the surviving male dosed with 1000 mg/kg. **Possible adverse effect indicated: ataxia in 1 male at 500 mg/kg and in 3 males and 2 females at 1000 mg/kg.** NOEL (M) < 125 mg/kg and NOEL (F) = 125 mg/kg based on a decrease in body weight gain and food consumption, and clinical signs. **Supplemental study** because only 5 animals were used per dose level, the animals were observed for only 3 days following dosing, and no FOB and neuropathology were performed on the test animals. (Corlett, 05/20/08)

Rat Acute Neurotoxicity Study

** **0029, 236783**; "Oral Acute Neurotoxicity Study of Flutriafol in Rats" (Barnett, J.F., Charles River Laboratories Preclinical Services, Horsham, PA, Study No. TQC00006, 12/01/06). 870.62. Flutriafol Technical (Lot No. UPL Bx 1 (2001), purity = 95.1%), suspended in corn oil, was administered in a single dose by gavage to 10 Crl:CD(SD) rats per sex per dose at dose levels of 0 (vehicle only), 125, 250, or 750 mg/kg. 4 males and 2 females at 750 mg/kg were moribund sacrificed on study days 2 or 3; all other animals survived until the scheduled sacrifice. Treatment-related slight ataxia was observed in 3 males at 750 mg/kg 8 hours after dosing during FOB assessment. Also, during this FOB assessment, treatment-related slightly drooping eyes and hunched posture were observed in both sexes at 750 mg/kg. None of these signs were observed in the animals during FOB assessments conducted 7 and 14 days after dosing. Also, treatment-related ptosis, dehydration, chromorhinorrhea, urine-stained abdominal fur, ungroomed coat, decreased motor activity, and lost or impaired righting reflex were observed during cageside observations in both sexes at 750 mg/kg. Treatment-related decreases in mean body weight and in mean food consumption were observed in males at doses beginning at 125 mg/kg and in females at doses beginning at 250 mg/kg between days 1 and 2. A treatment-related decrease (not statistically significant) in motor activity (both in the mean total number of movements and in the mean time spent in movement) was observed in both sexes at 750 mg/kg 8 hours and 7 days after treatment; this decrease was not observed 14 days after treatment. Necropsy revealed no treatment-related gross lesions. Neuropathological examination revealed no treatment-related abnormalities. **Possible adverse effect: ataxia in 3 males at 750 mg/kg.** NOEL (M) < 125 mg/kg and NOEL (F) = 125 mg/kg based on a decrease in body weight and food consumption, and clinical signs. **Acceptable.** (Corlett and Leung, 05/30/08)

Rat Subchronic Neurotoxicity Study

** 0030, 236784; "Oral (Diet) Subchronic Neurotoxicity Study of Flutriafol in Rats" (Barnett, J.F., Charles River Laboratories Preclinical Services, Horsham, PA, Study Number TQC00008, 02/01/07). 870.6200. Flutriafol technical, dry (CHA 131) (Lot number UPL Bx 1 (2001), purity = 95.1%) was admixed to the diet (using acetone) and fed to 10 Crl:CD(SD) rats per sex per dose at dose levels of 0, 500, 1500, or 3000 ppm (0, 28.9, 84.3, and 172.1 mg/kg/day, respectively for males and 0, 32.6, 97.6, and 185.0 mg/kg/day, respectively for females) for 92 consecutive days. No treatment-related mortalities occurred. No treatment-related clinical signs were observed during cageside observations that were conducted at least once daily. A treatment-related decrease in mean body weight gain between days 1 and 8 was observed in males at 1500 and 3000 ppm and in females at 3000 ppm and a treatment-related decrease in mean body weight gain between days 1 and 92 was observed in males at 3000 ppm and in females at 1500 ppm and 3000 ppm. A treatment-related decrease in mean food consumption was observed in both sexes at 1500 and 3000 ppm between days 1 and 8. FOB assessments revealed treatment-related decreases in mean body weight in males during week 2 and week 13 and in females during week 8 and week 13 at 3000 ppm. Motor activity assessments revealed no treatment-related effects. Neuropathological examination on the central and peripheral nervous systems revealed no treatment-related effects. No evidence of neurotoxicity was indicated. **No adverse effects.** NOEL (M) = 28.9 mg/kg/day (500 ppm) and NOEL (F) = 32.6 mg/kg/day (500 ppm) based on decreases in body weight gain and feed consumption. **Acceptable.** (Corlett and Leung, 06/25/08)

SUBCHRONIC STUDIES

0018; 236741; "PP450 (Flutriafol Technical): 28 Day Feeding Study in Rats" (Doe, J.E., Imperial Chemical Industries, PLC, Central Toxicology Laboratory, Macclesfield, Cheshire, UK, Laboratory Report No. CTL/P/684, **CTL Study No. PR0429**, 09/23/82). PP450 (batch P7, purity =

97%) was admixed to the diet and fed to 8 Wistar-derived Alderley Park rats per sex per dose at dose levels of 0, 100, 300, 800, 2000 or 5000 ppm (0, 10, 30, 80, 200, and 500 mg/kg/day, respectively, values calculated by the reviewer) for 28 days. One female at 5000 ppm was found dead on day 7. Animals at 5000 ppm were observed to be smaller and thinner than the control animals; ptosis, convoluted eyelids, chromolacrimation, stained snouts, signs of incontinence, hunched posture, and piloerection were also observed at 5000 ppm. A treatment-related decrease in mean body weight gain at 2000 and 5000 ppm and a decrease in mean food consumption at 5000 ppm in both sexes were observed. Treatment-related decreases in mean hematocrit and hemoglobin levels and a treatment-related increase in the mean white blood cell level in both sexes at 5000 ppm were observed. Treatment-related increases in the mean alanine transaminase concentration in males at 2000 and 5000 ppm and in females at 5000 ppm and in the mean aspartate transaminase concentration in both sexes at 5000 ppm levels were observed. A treatment-related increase in the mean aminopyrine-N-demethylase level in the liver of both sexes at 300 ppm and above was observed. A treatment-related increase mean relative liver weight in males at 100 ppm and above and in females at 300 ppm and above. Microscopic examination revealed treatment-related hepatocyte hypertrophy in males at dose levels of 800 ppm and above and in females at 2000 and 5000 ppm, fatty change in the liver in both sexes at 2000 and 5000 ppm, and hydropic degeneration in the liver in males at 2000 and 5000 ppm and in females at 5000 ppm. **No adverse effects.** NOEL (M) not determined (elevated mean relative liver weight at the lowest dose tested) and NOEL (F) = 10 mg/kg/day (100 ppm) based on an increase in liver weight, elevated liver enzymes, and microscopic findings in the liver. **Supplemental study** because individual test animal data were not presented in the test report. (Corlett, 05/15/08)

0019, 236742; “PP450 (Flutriafol Technical): 90 Day Feeding Study in Rats” (Pigott, G.H., Imperial Chemical Industries PLC, Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Laboratory Report No. CTL/P/744, CTL Study No. PR0432, 10/21/82). 870.3100. PP450 (batch assigned CTL reference number Y01433/003/010, purity = 93%) was admixed to the diet and fed to 20 Wistar-derived Alderley Park rats per sex per dose at dose levels of 0, 20, 200, or 2000 ppm (0, 2, 20, and 200 mg/kg/day, respectively, values calculated by the reviewer) for 90 days. No treatment-related mortalities occurred. No treatment-related clinical signs were observed during cageside observations that were conducted at least once daily. Treatment-related decreases in mean body weight gain and mean food consumption were observed in both sexes at 2000 ppm. Treatment-related decreases in mean hemoglobin and hematocrit levels in both sexes and in the mean red blood cell level in males were observed at 2000 ppm. A treatment-related increase in liver weight adjusted to body weight (determined by analysis of covariance) was observed in males at 2000 ppm and in females at 200 and 2000 ppm. A treatment-related increase in mean hepatic aminopyrine-N-demethylase activity was observed in both sexes at 200 and 2000 ppm. A treatment-related increase in smooth endoplasmic reticulum was observed in males at 200 and 2000 ppm and in females at 2000 ppm. Microscopic examination revealed treatment-related increased hepatocyte vacuolation in males at 200 and 2000 ppm and in females at 2000 ppm and centrilobular hypertrophy in both sexes at 2000 ppm in the liver. **No adverse effects.** NOEL (M/F) = 2 mg/kg/day (20 ppm) based on an increase in mean hepatic aminopyrine-N-demethylase activity, an increase in smooth endoplasmic reticulum, and centrilobular hypertrophy and hepatocyte vacuolation in the liver. **Acceptable.** (Corlett, 07/03/08)

0023; 236761; “Percutaneous Repeated Dose 14-Day Toxicity Dosage Range-Finding Study of Flutriafol in Rats” (Barnett, J.F., Charles River Laboratories Preclinical Services, Horsham, PA, Laboratory Project ID TQC00009, 06/30/06). Flutriafol (lot number UPL Bx 1 (2001), purity = 95.1%) was suspended in PEG 400 and applied to the clipped back of 5 Crl:CD(SD) rats per sex

per dose at dose levels of 0 (vehicle), 250, 500, and 1000 mg/kg/day for 6 hours daily for 14 days using an occlusive wrap. No animals died during the study. No treatment-related clinical signs were observed. No significant skin irritation was observed. No toxicologically related effects on body weight and food consumption were observed. Necropsy revealed no treatment-related abnormalities. **No adverse effects.** NOEL (systemic and skin, M/F) = 1000 mg/kg based on no effects at the highest dose tested. **Supplemental study** because only 5 animals per sex were used per dose level, the animals were dosed for only 14 days, and no hematology, clinical chemistry, ophthalmology, and histopathology were performed on the test animals. (Corlett, 08/11/08)

021, 236759; "Percutaneous Repeated Dose 28-Day Toxicity Study of Flutriafol in Rats" (Barnett, J.F., Charles River Laboratories Preclinical Services, Horsham, PA, Laboratory Project ID TQC00010, 01/31/07). 870.3200. Flutriafol Technical (Batch number UPL Bx 1 (2001), purity = 95.1%) was suspended in PEG 400 and applied to the clipped back of 10 Crl:CD(SD) rats per sex per dose at dose levels of 0 (vehicle), 250, 500, and 1000 mg/kg/day for 6 hours daily for 28 days. No animals died during the study interval. No treatment-related systemic clinical signs were observed. Treatment-related erythema and flaking of the skin at the test site were observed in males at 1000 mg/kg/day and in females at 500 and 1000 mg/kg/day. Examination of body weight and food consumption data revealed no treatment-related effects. Hematology revealed no treatment-related effects. Serum chemistry revealed no toxicologically-related or treatment-related effects. FOB and motor activity assessments revealed no treatment-related effects. No treatment-related effects on organ weights were observed. Necropsy revealed no treatment-related abnormalities. Microscopic examination revealed no treatment-related abnormalities in the organs or tissues to indicate any systemic toxicity. **No adverse effects.** NOEL (M/F, systemic) = 1000 mg/kg/day based on no effects at the highest dose tested; NOEL (M, skin) = 500 mg/kg/day and (F, skin) = 250 mg/kg/day based on erythema and flaking of the skin at the test site. **Acceptable.** (Corlett, 08/15/08)

0020, 236743; "PP450 (Flutriafol Technical): 90 Day Oral Dosing Study in Dogs" (Doe, J.E., Imperial Chemical Industries PLC, Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Laboratory Report No. CTL/P/733, CTL Study No. PR0433, 11/02/82). 870.3150. PP450 (batch number P10, purity = 93.0%) was administered by gelatin capsules to 4 beagle dogs per sex per dose at dose levels of 0 (one empty gelatin capsule), 1, 5, and 15 mg/kg/day daily for 90 days. No mortalities occurred. No treatment-related clinical signs were observed. A treatment-related decrease in mean body weight gain was observed in females at 15 mg/kg/day. Hematology and urinalysis revealed no treatment-related effects. A treatment-related increase in mean plasma alkaline phosphatase levels in both sexes at 15 mg/kg/day was observed at 4, 8, and 13 weeks. A treatment-related increase in liver weight adjusted to body weight (determined by analysis of covariance) was observed in both sexes at 15 mg/kg/day. A treatment-related increase in mean hepatic aminopyrine-N-demethylase activity was observed in both sexes at 5 and 15 mg/kg/day. Microscopic examination revealed a treatment-related slight increase in hemosiderin-laden Kupffer cells in the liver in both sexes at 15 mg/kg/day. **No adverse effects.** NOEL (M/F) = 1 mg/kg/day based on an increase in mean hepatic aminopyrine-N-demethylase activity. **Acceptable.** (Corlett, 07/10/08)

METABOLISM STUDIES

Metabolism, Rat

0032; 236788; "[^{14}C]-Flutriafol Metabolism in Rats after Single and Repeated Doses" (Millais, A.J., Huntingdon Life Sciences Ltd., Alconbury, Huntingdon, Cambridgeshire, England, Laboratory Project No. CHV 081/024050, 08/16/2004). 870.7485. Sufficient radiolabelled Flutriafol (Batch number: Rad 164, specific activity: 49.6 mCi/mmol, radiochemical purity > 97%)

and non-radiolabelled Flutriafol (lot number ASJ-10005-01, purity = 99.0%), formulated in polyethylene glycol 600, was administered by gavage to 4 Sprague Dawley (Crl:CD® (SD) IGS BR) rats per sex daily at a dose level of 5 mg/kg/day for 14 consecutive days; 4 additional rats per sex were administered a single dose of 250 mg/kg by gavage. In the repeated daily dose group, feces and urine were collected on days 1, 5, 10, 14, and every 24 hours for 168 hours after the 14th dose while urine and feces were collected from the single dose animals every 24 hours for 168 hours after the single dose. The primary route of elimination was in the urine. In the repeated daily dose male animals, 49.84 to 64.15 % of the radiolabelled dose was eliminated in the urine during the dosing interval and 168- hour interval following dosing while, in the female animals, 53.93 to 68.19% of the radiolabelled dose was eliminated in the urine during the same time intervals. Also, in the repeated daily dose male animals, 29.45 to 54.68 % of the radiolabelled dose was eliminated in the feces during the dosing interval and 168- hour interval following dosing while, in the female animals, 33.12 to 40.81% of the radiolabelled dose was eliminated in the feces during the same time intervals. In the single dose group animals, 60.64% and 67.53% of the radiolabelled dose was eliminated in the urine in the males and females, respectively and 33.06% and 26.92% of the radiolabelled dose was eliminated in the feces in the males and females, respectively, over the 168 hours following treatment. In the repeated daily dose group, the highest mean tissue concentrations of the radiolabelled dose were found in the whole blood (2.20 % daily dose in males, 0.75% in females), liver (0.70% in males, 0.25% in females), muscle (1.46% in males and 1.07% in females), and gastrointestinal tract and contents (0.74% in males and 0.10% in females). In the single dose group, the highest mean tissue concentrations of the radiolabelled dose were found in the whole blood (0.28 % dose in males, 0.21% in females), liver (0.05% in males, 0.03% in females), muscle (0.08% in males and 0.06% in females), and gastrointestinal tract and contents (0.33% in males and 0.10% in females). In addition to flutriafol, 19 regions (M1 through M19) were resolved by HPLC analysis of pooled urine and fecal extracts. In the repeated daily dose group, region M3, M5, M6, M8, M9, and M11 metabolites were the major radioactive metabolites detected in the urine of both sexes prior to enzyme treatment; after enzyme treatment, the region M15 metabolite emerged as the most prominent metabolite with region M8, M9, and M11 metabolites decreasing to background levels. In the single dose group, region M3, M5, M6, M8, and M15 metabolites were the major radioactive metabolites detected in the urine of both sexes prior to enzyme treatment; after enzyme treatment, the region M18 metabolite increased while the region M3 metabolite decreased to background levels. The primary site for metabolism of flutriafol was determined to be the 2-fluorophenyl ring. **Unacceptable but possibly upgradable** with the submission of the experimental results from the intravenous administration of the test material and measurement of radioactivity in the excreta and/or the results from the measurement of radioactivity in the bile since over 20% of the administered dose was found in the feces. (Corlett, 01/16/09)

0032; 236789; “PP450 (Flutriafol): Excretion and Tissue Retention of a Single Dose (5 mg/kg) in the Rat” (Jones, B.K., Imperial Chemical Industries PLC, Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Laboratory Report No. CTL/P/751, 10/07/82). PP450 (CTL Test Substance Control (TSC) reference Y01433/003/003/007, purity approximately 94%) and ^{14}C-labelled PP450 (TSC reference Y01433/012/001, specific activity= 2.17 Gbq/mM) formulated in polyethylene glycol 600, was administered in a single dose by gavage to 5 Alderley Park, Wistar-derived, rats per sex at a dose level of 5 mg/kg (specific activity of 373.03 kBq/mg). After dosing each animal was placed into an individual metabolism cage where the urine and feces were collected at 24-hour intervals for 7 days. 2 additional rats, 1 male and 1 female, designated for whole body autoradiography, were dosed once with 5 mg/kg at a higher specific activity (1.898MBq/mg). After dosing each of these 2 animals was placed into an individual metabolism cage where the expired carbon dioxide, urine, and feces were collected 24 and 48 hours after dosing. In the animals placed in metabolism cages for 7 days, mean radioactivity excreted in the urine was 45.39% and 51.72% for males and females, respectively and mean radioactivity excreted in the feces was 50.85% and 45.24% for males and females, respectively, after 7 days. In the animals placed in metabolism cages for 48 hours, radioactivity excreted in

the urine was 46.52% and 35.49% for males and females, respectively, radioactivity excreted in the feces was 41.40% and 61.92% for males and females, respectively, and radioactivity in expired CO_2 was 0.04% and 0.05% in the male and in the female, respectively, after 48 hours. In the animals placed metabolism cages for 7 days, less than 1% of the dose was present in the tissues and carcass of each animal. **Supplemental study** (metabolites were not characterized). (Corlett and Leung, 01/22/09)

0032; 236790; "Flutriafol: Biotransformation in the Rat" (Jones, B.K., Imperial Chemical Industries PLC, Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Laboratory Report No. CTL/P/856, Laboratory Study No. UR0149, 10/07/82). Two different ^{14}C-labelled forms of Flutriafol were used: ^{14}C-carbinol-labelled flutriafol (CTL reference Y01433/012/002, specific activity 2.17 Gbq/mmol) and ^{14}C-triazole-labelled flutriafol (CTL reference Y01433/004/001, specific activity 2.224 Gbq/mmol). Groups of male and female Alpk:AP rats, some with the bile duct cannulated, were administered a single dose of the test article, formulated in polyethylene glycol, by gavage. One group consisted of 6 female rats dosed with 250 mg/kg of ^{14}C-carbinol-labelled flutriafol. Another group, consisting of 2 males and 2 females with the bile duct cannulated, was dosed with 250 mg/kg of ^{14}C-carbinol-labelled flutriafol. A third group, consisting of 2 males and 2 females with the bile duct cannulated, was dosed with 5 mg/kg of ^{14}C-carbinol-labelled flutriafol. A fourth group, consisting of 2 males and 2 females with the bile duct cannulated, was dosed with 5 mg/kg of ^{14}C-triazole-labelled flutriafol. Urine, feces and/or bile were collected 24, 48, and 72 hours after dosing. In the group where females were dosed with 250 mg/kg of ^{14}C-carbinol-labelled flutriafol, % radioactivity recovered ranged from 57.63% to 64.39% in the urine and 15.32% to 26.65% in the feces over 72 hours. In the group where males and females were dosed with 250 mg/kg of ^{14}C-carbinol-labelled flutriafol, % radioactivity recovered ranged from 16.17% to 33.92% in the urine and from 44.10% to 72.02% in the bile over 72 hours. In the group where males and females were dosed with 5 mg/kg of ^{14}C-carbinol-labelled flutriafol, % radioactivity recovered ranged from 9.94% to 25.95% in the urine, from 0.77% to 6.54% in the feces, and from 51.67% to 81.18% in the bile over 72 hours. In the group where males and females were dosed with 5 mg/kg of ^{14}C-triazole-labelled flutriafol, % radioactivity recovered ranged from 20.65% to 26.68% in the urine, from 1.11% to 10.45% in the feces, and from 61.02% to 75.31% in the bile over 72 hours. Metabolites of flutriafol in the urine, feces, and bile were separated and characterized by HPLC, enzyme hydrolysis, ether extraction, TLC, GLC, mass spectrometry/gas chromatography, and NMR. Absorption and biotransformation of flutriafol was extensive with only trace amounts of parent flutriafol detected. All identified metabolites of flutriafol were shown to be hydroxylated derivatives of the o-fluorophenyl ring. **Supplemental study** (radioactivity in the organs and tissues of the test animals was not examined). (Corlett and Leung, 01/29/09)