CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Metconazole

Chemical Code # 5983 , **Tolerance** # 53063
SB 950 # NA

Original: 6/30/09
Revised: 8/25/09

I. DATA GAP STATUS

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

Toxicology one-liners are attached.

All record numbers through #248228 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T090825
Revised by T. Moore, 8/25/09

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

COMBINED, RAT

Study not submitted.

CHRONIC TOXICITY, RAT

**** 53063-0049; 248228**; "WL148271: A Two Year Chronic Toxicity Feeding Study in Rats"; (PJ.Y. Taupin; Sittingbourne Research Centre, Sittingbourne, Kent ME9 8AG, England; Report No. SBGR. 91.193; 9/16/92); Twenty Fischer 344.rats/sex/group received 10, 100, 300 or 1000 ppm of WL148271 (batch no. 89-01; purity: 95.3%) in the diet for 24 months ((M) 0.44, 4.29, 13.08, 43.95 mg/kg/day, (F) 0.52, 5.27, 15.98, 53.84 mg/kg/day). Forty animals/sex were included as a control group. Another cohort of 10 animals/sex/group received the test material in the diet at the same concentrations for 12 months. A control group of 20 animals/sex was included in this cohort. There was no treatment-related effect on the survival of the study animals. The mean body weights of both sexes in the 1000 ppm group were less than the control values throughout the study (p<0.01 or 0.05). The mean food consumption of both sexes in the 1000 ppm group was less than that of the control group over the course of the study. No treatment-related effects were evident in the hematological evaluation or urinalysis. In the clinical chemistry evaluation, serum bilirubin, cholesterol, and triglyceride levels and alkaline phosphatase activity of the 1000 ppm males were lower than those of the control group during the first 18 months of treatment (p<0.01). For the 1000 ppm females, the gamma glutamyl transpeptidase activity was greater than that of the control for the 1st 18 months of the study (p<0.01). The mean serum albumin levels and alanine aminotransferase activities of the 300 and 1000 ppm females were less than the control values during the first year of the study (p<0.01 or 0.05). In the necropsy examination, the mean liver and spleen weights (adjusted for terminal body weight) of both sexes in the 1000 ppm group were greater than those of the control group at both 12 and 24 months (NS, p<0.01 or 0.05). In the histopathology examination, centrilobular hypertrophy was noted in the livers of both sexes in the 1000 ppm group and the males in the 300 ppm group after 12 months of treatment and in the livers of the 1000 ppm males after 24 months of treatment. After 12 months, midzonal macrovesicular lipid vacuolation was evident in the livers of the 300 and 1000 ppm males and centrilobular macrovesicular lipid vacuolation was noted in the livers of the 1000 ppm females. At 24 months, an increased incidence of necrotic inflammatory foci was noted for the 100, 300 and 1000 ppm males (0: 2/40 vs. 100: 4/20, 300: 5/20, 1000: 5/20). In addition, increased incidences of clear cell foci and pigment deposition was reported for the 1000 ppm males. For the 1000 ppm females at 24 months, an increased incidence of fatty centribolular vacuolation was noted (0: 1/40 vs. 1000: 9/20). Histiocytic foci were evident in the spleen of both sexes of the 1000 ppm group after 24 months of treatment. In the adrenal glands of the 1000 ppm females, cortical hypertrophic foci were noted after 24 months. **Possible adverse effect:** necrosis and fat deposition in the liver; **Rat Chronic Dietary Toxicity NOEL:** (M) 10 ppm (0.44 mg/kg/day) (based upon the increased incidence of necrotic inflammatory foci in the liver of the 100 ppm males); (F) 100 ppm (5.27 mg/kg/day) (based upon treatment-related effects on several clinical chemistry parameters); **Study acceptable.** (Moore, 8/6/09)

CHRONIC TOXICITY, DOG

**** 53063-0044; 245733**; "WL148271: 52 Week Oral (Dietary Administration) Toxicity Study in the Beagle"; (H. Clay; Hazleton UK, Harrogate, North Yorkshire, HG3 IPY England; Study No. 579/24; 6/26/92); Four beagle dogs/sex/group received 0, 30, 300, 1000, or 3000 ppm of WL148271 (KNF-S-474m) (batch no. 89-01; purity: 95.3%) in the diet for 52 weeks ((M) 0, 1.09, 12.07, 39.0, 110.6 mg/kg/day, (F) 0, 1.10, 10.49, 36.8, 114.2 mg/kg/day). One male in the 3000 ppm group was euthanized in *extremis* due to poor health. The mean body weight gain of both sexes in the 3000 ppm group and of the males in the 1000 ppm group was less than the control values during the 1st 13 weeks of the study (p<0.01 or NS). This effect persisted for the 3000 ppm males through to the end of the study. There was no apparent treatment-related effect on food consumption. The urinalysis and hematology evaluations did not reveal any apparent treatment-related effects. In the ophthalmological examination, lens opacity was noted in the eyes of 3 males and 2 female in the 3000 ppm group by week 22 of the study. This effect persisted until

the end of the study. Lens opacity was also noted for 3 of the control females in the last ophthalmological examination at the termination of the study. In the clinical chemistry evaluation, the serum alkaline phosphatase activity levels of both sexes in the 1000 and 3000 ppm groups were elevated in comparison to the control values over the course of the treatment (p<0.05 or NS). The adjusted mean liver weights of both sexes in the 3000 ppm group were greater than the control values (NS). In the histopathological examination, hepatocytic hypertrophy of the liver was noted for both sexes in the 3000 ppm group ((M) 0: 0/4 vs. 3000: 3/3, (F) 0: 0:4 vs. 3000: 4/4). Kupffer cell pigment was also noted in the livers of both sexes in the 3000 ppm group and the females of the 1000 ppm group ((M) 0: 1/4 vs. 3000: 3/3, (F) 0: 1/4 vs. 1000: 3/4, 3000: 4/4). Lenticular degeneration was evident in the eyes of both sexes in the 3000 ppm group (M) 0: 0/4 vs. 3000: 3/3, (F) 0: 0/4 vs. 3000: 2/4). Increased hematopoiesis was evident in the spleens of both sexes in the 3000 ppm group ((M) 0: 0/4 vs. 3000: 3/3, (F) 0: 0/4 vs. 3000: 2/4). **Possible adverse effect:** lenticular degeneration of the eyes (cataract); **Dog Chronic Dietary Toxicity NOEL:** (M/F) 300 ppm ((M) 12.07 mg/kg/day, (F) 10.49 mg/kg/day) (based upon the increased serum levels of alkaline phosphatase for the 1000 ppm treatment group); **Study acceptable.** (Moore, 5/13/09)

ONCOGENICITY, RAT

** 53063-0046; 245735; "WL148271: A Two Year Oncogenicity Feeding Study in Rats"; (P.J.Y. Taupin; Sittingbourne Research Centre, Sittingbourne, Kent ME9 8AG, England; Report No. SBGR. 91.192; 7/30/92); Fifty Fischer 344 rats/sex/group received 0, 100, 300 or 1000 ppm of WL148271 (batch no. 89-01; purity: 95.3%) in the diet for 2 years ((M) 0, 4.61, 13.8, 46.5 mg/kg/day, (F) 0, 5.51, 16.6, 56.2 mg/kg/day). There was no treatment-related effect upon the survival of the study animals. The mean body weights of both sexes in the 1000 ppm group were less than those of the control group at various time points during the treatment period (p<0.01 or 0.05). The mean food consumption of both sexes in the 1000 ppm group was likewise less than that of the control animals at various time points during the study (p<0.01 or 0.05). In the 1000 ppm treatment group, the mean diameter of the erythrocytes of both sexes was less than that of the control group after 12 months and those of the males after 18 and 24 months of treatment (p<0.05 or 0.01). This reduction in diameter was associated with an altered cell morphology: microcytosis at 12, 18 and 24 months and anisocytosis and spherocytosis at 24 months. The mean adjusted liver weights of both sexes in the 1000 ppm group were greater than the control values (p<0.01). The mean adjusted kidney weight of the 1000 ppm males and the mean adjusted spleen weight of the 1000 ppm females were greater than the respective control values (p<0.05). In the histopathological examination, an increased incidence of clear cell foci, eosinophilic foci, and fatty vacuolated foci were noted in the livers of the 1000 ppm males. Fatty centrilobular vacuolation was noted in the livers of both sexes in the 1000 ppm group. Centrilobular hypertrophy and pigment deposition were evident in the livers of the males in the 300 and 1000 ppm groups. The livers of the 1000 ppm females also exhibited an increased incidence of clear cell foci. In the spleens of both sexes in the 1000 ppm group, an increased incidence of histocytic foci was noted. An increased incidence of cortical vacuolation was evident in the adrenal glands of the 300 and 1000 ppm males. Although an increased incidence of mononuclear cell leukemia was noted for the 1000 ppm females, the incidence was within the historical control range for the Fischer 344 rat and therefore not deemed to be treatment-related. **No adverse effect indicated. No oncogenicity was evident.** Study previously unacceptable**,** possibly upgradeable to acceptable with the calculation of test material uptake; data had been included in the report on pp. 516. **Study acceptable**. (Moore, 5/21/09, revised, Moore, 8/6/09)

ONCOGENICITY, MOUSE

**** 53063-0045; 245734**; "WL148271: 91 Week Oral (Dietary Administration) Carcinogeneity Study in the Mouse"; (H. Clay; Hazleton UK, Harrogate, North Yorkshire, HG3 IPY England; Study No. 579/26; 8/26/92); Fifty one Crl: CD-1 (ICR) Br mice/sex/group received 0, 30, 300 or 1000 ppm of WL148271 (KNF-S-474m); batch no. 89-01; purity: 95.3% (cis isomer: 79.8%, trans isomer: 15.5%) in the diet for 91 weeks ((M) 0, 4.22, 40.6, 144.9 mg/kg/day, (F) 0, 5.23, 53.0, 179.2 mg/kg/day). An additional 12 animals/sex/group received the diet for 12 months and were then euthanized. There was no treatment-related effect upon survival of the study animals. The mean body weight gain of the males was not affected after the 1st week of treatment. The mean body

weight gain of the females in the 1000 ppm group was less than that of the control group over the course of the study (p<0.05). The mean food consumption of the 1000 ppm males was less than that of the control group during the 1st week of the study and was not affected thereafter. The mean food consumption of the 1000 ppm females was less than that of the control group at various time intervals during the 91-week treatment period (p<0.001 or 0.05). In the hematology evaluation, the mean total white blood cell, neutrophil and lymphocyte counts of both sexes in the 1000 ppm group were greater than the control values after 91 weeks of treatment (p<0.001, 0.01 or 0.05). In the clinical chemistry evaluation, the mean aspartate aminotransferase and alanine aminotransferase activities in the serum were elevated for both sexes in the 1000 ppm group at 52 and 91 weeks (p<0.001). The mean serum cholesterol and triglyceride levels of both sexes in the 1000 ppm group were less than the control values after 52 weeks of treatment (p<0.001, 0.01 or 0.05). The effect on the triglyceride levels persisted through the 91-week treatment period (p<0.01 or 0.05). The mean absolute and relative liver weights of both sexes in the 1000 ppm group were greater than those of the control group after 52 and 91 weeks of treatment (p<0.001). The mean absolute and relative liver weights of the 300 ppm females were greater than the control values after 52 weeks of treatment (p<0.05 or 0.001). The mean absolute and relative spleen weights of both sexes in the 1000 ppm group were less than the control values after both 52 and 91 weeks of treatment (p>0.05 or NS). In the histopathological examination, an increased incidence of vacuolation was noted in the liver of the females in the 300 and 1000 ppm group after 52 weeks of treatment and in both sexes of the 300 and 1000 ppm groups after 91 weeks (52 weeks (F) 0: 5/12 vs. 300: 10/12, 1000: 10/12; 91 weeks (M) 0: 11/50 vs. 300: 20/51, 1000: 37/51, (F) 0: 11/50 vs. 300: 36/51, 1000: 44/51). Hepatocytic hypertrophy was noted in the livers of both sexes in the 300 and 1000 ppm groups after 52 and 91 weeks (52 weeks (M) 0: 0/12 vs. 300: 9/12, 1000: 11/11, (F) 0: 0/12 vs. 300: 3/12, 1000: 10/12, 91 weeks (M) 0: 0/50 vs. 300: 13/51, 1000: 44/51, (F) 0: 0/50 vs. 300: 8/51, 1000: 38/51). Sinusoidal hypercellularity/single cell necrosis/pigmentation was noted in the liver of both sexes in the 300 and 1000 ppm groups after both 52 and 91 weeks (52 weeks (M) 0: 0/12 vs. 300: 2/12, 1000: 9/11, (F) 0: 0/12 vs. 300: 3/12, 1000: 11/12, 91 weeks (M) 0: 0/50 vs. 300: 10/51, 1000: 37/51, (F) 0: 0/50 vs. 300:18/51, 1000: 35/51). Oval cell hyperplasia was noted in the livers of the 1000 ppm females after 52 weeks of treatment and of both sexes in the 1000 ppm group after 91 weeks (52 weeks (F) 0: 0/12 vs. 1000: 2/12, 91 weeks (M) 0: 0/50 vs. 1000: 12/51, (F) 0: 0/50 vs. 1000: 14/51). Biliary proliferation was evident in the livers of both sexes in the 1000 ppm group after 91 weeks ((M) 0/50 vs. 1000: 8/51, (F) 0: 0/50 vs. 1000: 13/51). Multifocal hyperplasia was identified in the livers of the females in the 1000 ppm group after 52 weeks and in both sexes after 91 weeks (52 weeks (F) 0: 0/12 vs. 1000: 9/12, 91 weeks (M) 0: 0/50 vs. 1000: 31/51, (F) 0: 0/50 vs. 1000: 44/51). Atrophy and prominent trabeculae and stroma were noted for the spleens of both sexes in the 1000 ppm group after 52 and 91 weeks and for both sexes in the 300 ppm group after 91 weeks (52 weeks (M) 0/12 vs. 1000: 8/11, (F) 0: 0/12 vs. 1000: 10/12, 91 weeks (M) 0: 1/49 vs. 300: 9/49, 1000: 39/50, (F) 0: 0/50 vs. 300: 15/50, 1000: 41/49). An increased incidence of corticomedullary pigment was evident in the adrenal glands of both sexes in the 300 and 1000 ppm groups after 52 weeks of treatment ((M) 0: 2/12 vs. 300: 5/12, 1000: 9/11, (F) 0: 4/12 vs. 300: 11/11, 1000: 12/12). This effect was not evident after 91 weeks. An increased incidence of liver adenomas was noted for the 1000 ppm females after 52 weeks and for both sexes in the 1000 ppm group after 91 weeks of treatment (52 weeks (F) 0: 0/12 vs. 1000: 8/12, 91 weeks (M) 0: 10/50 vs. 1000: 34/51, (F) 0: 0/50 vs. 1000: 42/51). **Possible adverse effect:** liver oncogenicity; **Mouse Chronic Dietary NOEL:** (M/F) 30 ppm ((M) 4.22 mg/kg/day, (F) 5.23 mg/kg/day) (based upon treatment-related effects on the liver of both sexes in the 300 ppm group); **Liver oncogenicity**; **Study acceptable.** (Moore, 5/19/09)

REPRODUCTION, RAT

**** 53063-0008; 239046**; " KNF-474m: Reproductive Toxicity Study in Rats"; (S. Teramoto; The Institute of Environmental Toxicology, Mitsukaido-shi, Ibaraki 303-0043, Japan; Project ID. IET 00-0146; 6/6/02); In a two-generation reproduction study, 24 Crj:CD (SD)[IGS] rats/sex/group in the F0 generation received 0, 30, 150, or 750 ppm of KNF-474m (lot no. 9Z521; purity: 98.99%) in the diet for 10 weeks prior to mating, during mating, and during the 3 weeks each of gestation and lactation. At that time, 24 F1 animals/sex/group were selected as parents and treated with the same dosing regimens for 10 weeks, followed by mating and 3 weeks each for gestation and

lactation of the F2 generation ((M) **F0**: 0, 1.73, 8.49, 43.2 mg/kg/day, **F1**: 0, 1.81, 9.05, 45.7 mg/kg/day, (F) **F0**: **premating:** 0, 2.14, 10.78, 53.2 mg/kg/day, **gestation:** 0, 1.71, 8.58, 43.4 mg/kg/day, **lactation:** 0, 4.72, 24.2, 116.5 mg/kg/day, **F1**: **premating:** 0, 2.20, 11.21 55.5 mg/kg/day; **gestation:** 0, 1.64, 8.41, 42.9 mg/kg/day, **lactation:** 0, 4.43, 21.8, 102.9 mg/kg/day). Five F0 dams and four F1 dams in the 750 ppm group died during the delivery of their litters. The mean body weight gains of the parental rats of both sexes in the 750 ppm group of both generations were less than the control values at some time during the premating period (p<0.001, 0.01, 0.05 or NS). The mean food consumption for the F0 and F1 females and the F1 males in the 750 ppm group was less than the control animals at various times during the treatment period (p<0.001 or 0.05). The mean relative liver weight of both sexes in the 750 ppm group of both generations were greater than the control values (p<0.001, 0.01, 0.05, NS). The mean absolute liver weight of the F1 females in the 750 ppm group was also greater than that of the control (p<0.05). The mean absolute brain weight of the F1 females in the 750 group was less than the control value (p<0.001). No treatment-related lesions were evident in the reproductive tissues and organs of either generation. In the liver, fatty change in the centrilobular hepatocytes was noted for the F0 and F1 males of the 750 ppm group. The F0 and F1 females of the 750 ppm group exhibited centrilobular hepatocytic hypertrophy. In addition, 4 of the 5 F0 dams and 3 of the 4 F1 dams in the 750 ppm group which died during the delivery of their litters demonstrated diffuse cortical cell hypertrophy of the adrenal gland. Congestion of the spleen was also noted for the F1 females in the 750 ppm group. There was no apparent treatment-related effect upon the number of sperm and their morphology or motility for either generation. No treatment-related effect upon time to vaginal opening or preputial separation was evident for the F1 generation. The length of gestation was extended for the F0 and F1 females in the 750 ppm group (p<0.01 or NS). Death of 5 F0 and 4 F1 dams in the 750 ppm group occurred during the delivery. The fertility and gestation indices for the F0 dams and the gestation index for the F1 dams of the 750 ppm group were less than the control values. The mean litter sizes of the F0 and F1 dams in the 750 ppm group were less than those of the control group. In the developmental phase of the study, the mean body weight gain of the 750 ppm offspring in both generations was less than that of the control during the lactation period (p<0.001, 0.01, 0.05 or NS); the mean relative spleen weights of the weanlings of both sexes in both generations of the 750 ppm group were greater than the control values (p<0.001, 0.01, 0.05 or NS). The mean absolute brain weights of both sexes of weanlings in both generations of the 750 ppm group were less than those of the control (p<0.001). However, the mean relative brain weights were unaffected by the treatment. **Possible adverse effect:** death of the dams at the time of delivery. **Parental NOEL:** (M/F) 150 ppm ((M) 8.49 mg/kg/day, (F) 10.78 mg/kg/day) (based upon lower body weight gain and lesions in the liver of both sexes in both generations of the 750 ppm group); **Reproduction NOEL:** 150 ppm (8.41 mg/kg/day) (based upon smaller litter size and maternal deaths at the time of delivery for the dams in the 750 ppm group); **Developmental NOEL:** 150 ppm (21.8 mg/kg/day) (based upon lower mean body weights for the pups of both generations in the 750 ppm group); **Study acceptable**. (Moore, 1/30/09)

53063-0008; 239045; "WL 148271: Preliminary Study to Assess Effects on Reproductive Performance in Rats"; (C.R. Willoughby; Life Science Research Ltd., Suffolk, IP23 7PX, England; Report No. 91/0109; 7/3/91); Six CD (Sprague-Dawley) rats/sex/group received 0, 1, 2, 8 or 32 mg/kg/day of WL 148271 (batch no. 89-01; purity: 95.3% (1/25/89), 96.3% (7/13/89), 96.2% (3/12/91)) in the diet for a two-week premating period, mating, 20-day gestation period and a 4-week lactation period. The offspring received the test material for an additional 4 weeks (to 8 weeks post-partum). No parental deaths resulted from the treatment. The mean body weights and food consumption were not affected by the treatment. There was no treatment-related effect upon reproductive parameters. The development of the offspring was not affected by the treatment. **No adverse effect indicated. Parental NOEL:** 32 mg/kg/day (based on the lack of treatment-related effects on both sexes in the 32 mg//kg treatment group); **Reproductive NOEL:** 32 mg/kg/day (based on the lack of treatment-related effects on reproductive parameters for the 32 mg//kg treatment group); **Developmental NOEL:** 32 mg/kg/day (based upon the lack of treatment-related effects on the development of the offspring in the 32 mg//kg treatment group); **Study supplemental** (non-guideline study). (Moore, 1/27/09)

TERATOLOGY, RAT

** 53063-0007; 239041; "KNF-S-474m: Teratology Study by Oral Gavage Administration to CD Rats"; (S.M. Fulcher; Huntingdon Life Sciences Ltd., Alconbury, Huntingdon, Cambridgeshire, PE28 4HS, England; Project ID. KRA/069 022919; 10/30/02); Twenty two mated female CD (Sprague-Dawley) rats were dosed orally by gavage with 0 (aqueous 1% methylcellulose), 1, 4, 16, or 64 mg/kg/day from gestation day 6 through gestation day 19. One dam in the 64 mg/kg group was euthanized for humane reasons on day 18 of gestation. The mean body weight gain and food consumption of the dams in the 64 mg/kg group were less than the control values throughout the treatment period (p<0.01). The numbers of both early and late resorptions in the 64 mg/kg group was greater than the control values (p<0.05, 0.001). The mean fetal weights of the 64 mg/kg group were less than the control weights (p<0.01). The mean placental weights of the 16 and 64 mg/kg groups were greater than the control values (p<0.05 or 0.01). The fetuses in the 64 mg/kg group demonstrated various visceral anomalies which were not present in the other treatment groups (septal defect in the ventricle of the heart, variation in the origin of the subclavian vein, green deposits in the ureter of the kidneys). (Note: these green deposits were identified as lipofuscins). **No adverse effect indicated. Maternal NOEL:** 16 mg/kg/day (based upon lower mean body weights and food consumption for the 64 mg/kg dams) **Developmental NOEL:** 16 mg/kg/day (based upon the lower mean fetal body weights, increased incidence of early and late resorptions and incidence of visceral anomalies in the fetuses of the 64 mg/kg group); **Study acceptable.** (Moore, 12/10/08)

53063-0007; 239040; "KNF-S-474m: Preliminary Teratology Study by Oral Gavage Administration to CD Rats"; (S.M. Fulcher; Huntingdon Life Sciences Ltd., Alconbury, Huntingdon, Cambridgeshire, PE28 4HS, England; Project ID. KRA 064/020002; 7/17/02); Six mated female Sprague-Dawley rats/group were dosed orally by gavage with 0 (aqueous 1% methylcellulose), 4, 16, or 64 mg/kg/day of KNF-474m (metconazole technical) (lot no. 9Z521; purity: 98.99%) from gestation day 6 through gestation day 19. No maternal deaths resulted from the treatment. The mean body weight gain of the 64 mg/kg dams was less than that of the control over the course of the treatment period. Their food consumption was also less than that of the control animals over most of the treatment period. The mean fetal weight of the 64 mg/kg group was 84% of the control weight. Swollen and/or mottled placentas were noted in the 16 and 64 mg/kg groups. Some of the fetuses in the 64 mg/kg treatment group had shiny translucent skin. **No adverse effect noted. No NOEL assigned. Study supplemental** (non-guideline study). (Moore, 12/9/08)

TERATOLOGY, RABBIT

** 53063-0043; 245732; "A Definitive Oral Developmental Toxicity (Embryo-Fetal Toxicity/Teratogenicity) Study with AC 900768 in Rabbits"; (A.M. Hoberman; Argus Research Laboratories, Inc., Horsham, PA; Report No. 101-027; 5/8/97); Twenty five mated female New Zealand white rabbits/group were dosed orally by gavage with 0, 5, 10, 20 or 40 mg/kg/day of AC 900768 (Metconazole Technical) (lot no. AC 10575-61; purity: 98.3%) from day 6 through day 28 of gestation. Two does, one in the control group and one in the 40 mg/kg group died as a consequence of intubation errors. There was no treatment-related effect on either the mean body weight gain or food consumption. The mean hemoglobin concentration, hematocrit and corpuscular volume of the 400 mg/kg does were less than the control values (p<0.01 or 0.05). The serum alkaline phosphatase activity level of the 40 mg/kg group was greater than that of the control (p<0.05). The mean relative liver weight of the 40 mg/kg does was greater than that of the control group (NS). No treatment-related lesions were noted in the liver. In fetal development, there was an increased incidence of both early and late resorptions in the 40 mg/kg group. The mean body weight of the 40 mg/kg fetuses was less than that of the control group (NS). No treatment-related fetal alterations were noted. **No adverse effect indicated. Maternal NOEL:** 20 mg/kg/day (based upon treatment-related effects upon various hematology and clinical chemistry parameters in the 40 mg/kg group); **Developmental NOEL:** 20 mg/kg/day (based upon the increased incidence of fetal resorptions and lower mean fetal weights); **Study acceptable.** (Moore, 5/11/09)

53063-0008; 239043; "An Oral Development (Embryo-Fetal Toxicity/Teratogenicity) Pilot Study with AC 900,768 in Rabbits"; (A.M. Hoberman; Argus Research Laboratories, Inc., Horsham, PA;

Project ID. ARGUS 101-027P; 12/2/96); Ten mated New Zealand white female rabbits were dosed orally by gavage with 0 (vehicle:aqueous 0.5% carboxymethylcellulose), 1, 5, 10, 20 or 40 mg/kg/day of AC 900,768 (Metconazole Technical) (lot nos. AC 10575-61 and AC9339-114; purity: 98.3%) from day 6 through day 28 of gestation. No deaths occurred during the study. No treatment-related effect was noted on the mean body weight gain or food consumption. The incidence of late resorptions was increased in the 40 mg/kg group. No treatment-related effect on fetal body weights was evident. The incidence of fetal alterations was not treatment-related. **Possible adverse effect:** increased incidence of late resorptions; **Maternal NOEL:** 40 mg/kg/day (based upon the lack of treatment-related effects on the 40 mg/kg does); **Developmental NOEL:** 20 mg/kg/day (based upon the increased incidence of late fetal resorptions in the 40 mg/kg group); **Study supplemental** (non-guideline study). (Moore, 1/22/09)

GENE MUTATION

** 53063-0047; 245736; "Bacterial Mutagenicity Studies with WL148271 (KNF-S-474M)"; (T.M. Brooks, D.E. Wiggins; Sittingbourne Research Centre, Sittingbourne, Kent ME9 8AG, England; Report No. SBGR.90.190; 10/11/90); *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 and *Escherichia coli* strain WP2 *uvrA* were exposed to concentrations of WL148271 (KNF-S-474m) (lot no. 89-01, purity: 95.3%) ranging from 31.25 to 5000 ug/plate under conditions of non-activation and activation. The cells were exposed to the test material for 48 to 72 hours at 37° C, using the plate incorporation procedure. Each treatment level was performed in the triplicate with two trials. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. **No adverse effect indicated.** There was no increase in the incidence of revertant colonies under conditions of either activation or non-activation. Positive controls were functional. **Study acceptable.** (Moore, 5/22/09)

** 53063-0047; 245737; "WL136184 (KNF-S-474c): Bacterial Mutagenicity Studies"; (T.M. Brooks, D.E. Wiggins; Sittingbourne Research Centre, Sittingbourne, Kent ME9 8AG, England; Report No. SBGR.91.071; 4/22/91); *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 and *Escherichia coli* strain WP2 *uvrA* were exposed to concentrations of WL136184 (KNF-S-474c) (cis-isomer of Metconazole) (batch no. 12, purity: 95.2%) ranging from 31.25 to 5000 ug/plate under conditions of non-activation and activation. The cells were exposed to the test material for 48 to 72 hours at 37° C, using the plate incorporation procedure. Each treatment level was performed in the triplicate with two trials. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. **No adverse effect indicated.** There was no increase in the incidence of revertant colonies under conditions of either activation or non-activation. Positive controls were functional. **Study acceptable.** (Moore, 5/22/09)

** 53063-0063; 245739; "Study to Determine the Ability of WL 136184 (KNF-s-474c) to Induce Mutations at the Thymidine Kinase (tk) Locus in Mouse Lymphoma L5178Y Cells Using a Fluctuation Assay"; (J. Clements; Hazleton Microtest, Heslington, York, Y01 5DU, England; Study No. SRS 3/TK; 12/17/91); Mouse lymphoma L5178Y cells were treated with WL136184 (KNF-S-474c) (cis-isomer of Metconazole) (batch no. 12, purity: 95.2%) at concentrations ranging from 12.5 to 125 ug/ml under conditions of both non-activation and activation for 3 hours at 37° C in the first trial. In the second trial, the cells were exposed to concentrations ranging from 20 to 70 ug/ml under conditions of non-activation and from 12.5 to 90 ug/ml under conditions of activation. Duplicate cultures/treatment level were included in the study. An Aroclor 1254-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 control. There was no dose-related increase in mutation frequency under conditions of activation or non-activation. Positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 5/26/09)

CHROMOSOME EFFECTS

** 53063-0047; 245738; "Study to Evaluate the Potential of WL136184 (KNF-S-474c) to Induce Micronuclei in the Polychromatic Erythrocytes of CD-1 Mice"; (R. Marshall; Hazleton Microtest, Heslington, York, Y01 5DU, England; Study No. SRS 3/MNT; Ten CD-1 mice/sex/group were dosed orally by gavage with 0 (vehicle: aqueous 0.5% (w/v) carboxymethyl cellulose), 75, 150 or

300 mg/kg of WL136184 (KNF-S-474c) (cis-isomer of Metconazole); (batch no. 12, purity: 95.2%) on two consecutive days. Five animals/sex/time point were euthanized at 24 and 48 hours post-final dose. In addition, 5 animals/sex were dosed with 80 mg/kg of cyclophosphamide (positive control) and euthanized at 24 hours post-dose. Bone marrow samples from the femurs of each animal were examined and 2000 polychromatic erythrocytes (PCE) per animal were examined for micronuclei. The ratio of PCE's to normochromatic erythrocytes (PCEs/NCE) was calculated as well. There was no treatment-related increase in the number of PCE's with a micronucleus. **No adverse effect indicated.** The positive control was functional. **Study acceptable.** (Moore, 5/26/09)

** 53063-0047; 245740; "WL136184 (KNF-S-474c): *In Vitro* Chromosome Studies Using Human Lymphocytes; (T.M. Brooks, D.E. Wiggins; Sittingbourne Research Centre, Sittingbourne, Kent, ME9 8AG, England; 10/23/91); Primary human lymphocyte cultures, procured from the whole blood of volunteers (stimulated with PHA for 48 hours), were treated with concentrations of WL136184 (KNF-S-474c) (cis-isomer of Metconazole) (batch no. 12, purity: 95.2%) ranging from 23.44 to 750 ug/ml for 3 hour (plus an additional 21 hours of incubation) and from 2.93 to 750 ug/ml for 24 and 48 hours under conditions of non-activation. Under conditions of activation, the cells were exposed to concentrations of the test material ranging from 93.75 to 750 ug/ml for 3 hours (plus an additional 21 hours of incubation). A single trial was performed with duplicate samples per treatment level. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. No treatment-related increase in chromosomal aberrations was evident in the assay. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 5/27/09)

**** 53063-0047; 245741;** "WL148271 (KNF-S-474m): *In Vitro* Chromosome Studies"; (T.M. Brooks, D.E. Wiggins; Sittingbourne Research Centre, Sittingbourne, Kent, ME9 8AG, England; Report No. SBGR.90.290; 2/22/91); Chinese Hamster Ovary cells (K_1-BH_4) were incubated with WL148271 (KNF-S-474m) (batch no. 89-01; purity: 95.3% (cis isomer: 79.8%, trans isomer: 15.5%)) for 24 hours at concentrations ranging from 1.56 to 25 ug/ml and for 48 hours at concentrations ranging from 0.625 to 10 ug/ml under conditions of non-activation. Under conditions of activation, cells were exposed to the test material for 3 hours and then incubated for an additional 21 hours at concentrations ranging from 6.25 to 400 ug/ml or exposed to the test material for 3 hours and then incubated for an additional 45 hours at concentrations ranging from 4.375 to 35 ug/ml. In all of the assays, the cells were incubated the last 2 hours with Colcemid prior to fixation. All of the incubations were performed with duplicate cultures. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no apparent treatment-related increase in the percentage of cells with chromosomal aberrations under conditions of non-activation. A treatment-related increase in cells with aberrations was noted under conditions of activation. The positive controls marginally functional. **Possible adverse effect:** clastogenicity evident under conditions of activation. **Study acceptable.** (Moore, 5/28/09)

** 53063-0047; 245742; "*In Vivo* Test for Chemical Induction of Micronucleated Polychromatic Erythrocytes in Mouse Bone Marrow Cells-CL 900,768"; (J. Xu; SITEK Research Laboratories, Rockville, MD; Study No. 0312-1521; 3/9/95); Fifteen CD-1 mice/sex/group were dosed orally by gavage with 0 (vehicle: aqueous 0.5% (w/v) carboxymethyl cellulose), 400, 1000 or 2000 mg/kg of CL 900,768 (Metconazole technical) (lot no. AC 9339-114; purity: 97.9%). Five animals/sex/time point were euthanized at 24, 48, and 72 hours post-dose. In addition, 5 animals/sex were dosed with 1 mg/kg of triethylenemelamine (positive control) and euthanized at 24 hours post-dose. Bone marrow samples from the femurs of each animal were examined and 2000 polychromatic erythrocytes (PCE) per animal were examined for micronuclei. The ratio of PCE's to normochromatic erythrocytes (PCEs/NCE) was calculated as well. There was no treatment-related increase in the number of PCE's with a micronucleus. **No adverse effect indicated.** The positive control was functional. **Study acceptable.** (Moore, 5/29/09)

DNA DAMAGE

** 53063-0047; 245743; "Test for Chemical Induction of Unscheduled DNA Synthesis in Rat Primary Hepatocytes Obtained from Rats Treated *In Vivo* - CL 900,768"; (K.J. Pant; SITEK

Research Laboratories, Rockville, MD; Study No. 0312-5220; 3/9/95); Six Sprague-Dawley male rats/group received a single oral dose of 0 (aqueous 0.5% carboxymethyl cellulose), 400, 1000 or 2000 mg/kg of CL 900,768 (Metconazole technical) (lot no. AC 9339-114; purity: 97.9%) by gavage. Hepatocytes from 3 animals/group/time point were isolated at 4 and 16 hours post-dose. Cells were exposed to (methyl-^{3}H) thymidine for 18 hours. One hundred fifty cells were scored per animal. No increase in the net nuclear grain counts was evident at any dose level or either sampling time. **No adverse effect indicated**. The positive controls were functional. **Study Acceptable**. (Moore, 6/1/09).

** 53063-0047; 245744; "Study to Evaluate the Potential of WL136184 (KNF-S-474c) to Induce Unscheduled DNA Synthesis in Rat Liver Using an *In Vivo/In Vitro* Procedure"; (S.W. Dean; Hazleton Microtest, Heslington, York, Y01 5DU, England; Study No. SRS 3/ILU; 7/11/91); Six male Wistar rats/group/time point were dosed orally by gavage with 0 (aqueous 0.5% (w/v) carboxymethyl cellulose), 443 or 1400 mg/kg of WL136184 (KNF-S-474c) (cis-isomer of Metconazole) (batch no. 12; purity: 95.2%) and euthanized 2 to 3 hours or 12 to 13 hours after dosing. As positive controls, 6 males/group were treated with 10 mg/kg of dimethynitrosamine and euthanized 2 to 3 hours post-dose or 50 mg/kg of 2-acetamidofluorene and euthanized 12 to 13 hours after dosing. Upon recovery of the hepatocytes, a primary culture was established and the cells were exposed to ^{3}H-thymidine (10 uCi/ml) for 4 hours, followed by further incubation overnight with unlabeled thymidine. Two cultures/animal, 25 cells/culture, five animals/treatment level, were evaluated for the number of net grains/nucleus. There was no treatment-related increase in unscheduled DNA synthesis. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 6/2/09)

NEUROTOXICITY

Guideline study not submitted.

METABOLISM STUDIES

53063-0009; 239052; "Metabolism of KNF-474m in Rats"; (E. Yamamoto; The Institute of Environmental Toxicology, Mitsukaido-shi, Ibarakii, 303-0043, Japan; Project ID. IET01-8002; 8/16/02); In this study, the pharmacokinetics and tissue distribution of metconazole was evaluated. In the pharmacokinetic phase, three Fisher 344/DuCrj rats/sex/group were dosed orally by gavage with 2 or 200 mg/kg of [Cyclopentyl-^{14}C]KNF-474 (lot no. CP-2397, specific activity: 1.83 GBq/mmol, radiochemical purity: 98.8% (cis/trans isomeric ratio: 85/15)). The specific activity of the dosing preparations was adjusted by using unlabeled KNF-474m (lot no. 9Z521, purity: 98.99% (cis/trans isomeric ratio: 83/16)) in the preparations. Blood samples were drawn from an in-dwelling catheter up to 72 hours post-dose for the 2 mg/kg group and up to 120 hours post-dose for the 200 mg/kg group. In the tissue distribution study, 9 rats/sex were treated with a single dose of 2 mg/kg (Group A), 12 animals/sex were treated with a single dose of 200 mg/kg (Group B) and 6 animals/sex were treated for 14 days with 2 mg/kg/day of the radiolabeled test material (Group C). For Group A, 3 animals/sex/time point were euthanized at 0.5, 24 and 72 hours post-dose. For Group B, 3 animals/sex/time point were euthanized at 4, 24, 72 and 120 hours post-dose. For Group C, 3 animals/sex/time point were euthanized at 0.5 and 72 hours post-final dose. In the pharmacokinetic study, the time to peak plasma levels was 0.25 and 4 hours post-dose for the 2 and 200 mg/kg treatment groups, respectively. The biological half-lives for the β elimination phase were 20 and 34 hours for the males and females, respectively, in the 2 mg/kg group and 25 and 34 hours for the males and females, respectively, in the 200 mg/kg group. The liver was the organ in which the greatest percentage of the administered dose was recovered. The liver and the adrenal gland had the highest concentrations of the radiolabel for the 2 and 200 mg/kg treatment groups. For the 200 mg/kg treatment group, the concentrations of radiolabel in the kidneys, thyroid gland, skin and hair, and adipose tissue were also relatively high over the 120-hour assay period. The concentrations of radiolabel in the brain, heart, pituitary gland, lung, prostate, seminal vesicles and testes of this group were high during the first 24 to 72 hours post-dose but the levels had appreciatively diminished by 120 hours. At the conclusion of the 14-day treatment regimen of 2 mg/kg/day, the concentrations of radiolabel in the liver and adrenal glands were the highest among the assayed

tissues. Multiple dosing resulted in greater residual concentrations of the radiolabel in each of the assayed tissues/organs. The biological half-lives of the radiolabel in the liver, kidneys, adipose tissue, and plasma ranged between 14 and 43 hours for the three different dosing regimens. The biological half-life for the radiolabel in the adrenal gland of the males in both groups A and C were greater than that range. The biological half-live in the erythrocytes of the Group C males and females was extended to 90 and 79 hours, respectively. **Supplemental Study.** (Moore, 3/2/09)

53063-0017; 240853; "The Fate of [Cyclopentyl-^{14}C]WL148271 in the Fischer 344 Rat following a Single Low Oral Dose of 2 mg per kg. I. Elimination and Distribution"; (B.J. Morrison, K.A. Richardson; Sittingbourne Research Centre, Biotechnology and Toxicology Directorate, Kent ME9 8AG, England; Report No. SBGR.90.016; 9/10/90); Five Fischer 344 rats/sex were dosed orally by gavage with 2 mg/kg of [Cyclopentyl-^{14}C]WL148271 (KNF-S-474m (batch no. S1106/1, radiochemical purity: 99.3%, chemical purity: >99%; specific activity: 31.09 uCi/mg, isomeric ratio: 79/21 cis/trans). The specific activity of the dosing preparation was adjusted by supplementation with unlabeled KNF-S-474m (batch no. not identified, purity not identified). Urine and fecal samples were collected up to 3 days post-dose. The distribution of radiolabeling in specific tissues/organs was assayed at that time. The predominant route of excretion was via the feces. Eighty and 67% of the administered dose was excreted in the feces for the males and females, respectively. Fifteen and 26% of the dose was recovered in the urine of the males and females, respectively. Sixty one and 54% of the dose was recovered in the 1st 24 hours post-dose for the males and females, respectively. The adrenal gland was the organ with the highest concentration of the radiolabel. The liver and gastrointestinal tract were the other two sites with higher levels of radioactivity. All of the other tissues were below 0.046 ug equivalents/gram of tissue. **Study supplemental.** (Moore, 2/18/09)

53063-0017; 240854; "[Cyclopentyl-^{14}C]WL148271 (KNF-S-474m): Fate in the Fischer 344 Rat following a Single Oral Low Dose of 2 mg/kg. II. Metabolite Identification"; (K.A. Richardson; Sittingbourne Research Centre, Sittingbourne, Kent ME9 8AG, England; Report No. SBGR.91.154; 12/2/91); Urine, fecal and liver samples derived from the study submitted under record no. 240853 were analyzed for the presence of specific radiolabeled metabolites of the test material. Thin layer chromatography and high pressure liquid chromatographic techniques were used to isolate and identify the metabolites. Metabolites in the urine and liver could not be elucidated. The metabolites which were isolated and identified in the feces were hydroxylated moieties of the parent compound. Two of the seven metabolites were further oxidized to the carboxylate. The identified moieties comprised 35 and 47% of the administered dose for the males and females, respectively. **Supplemental Study.** (Moore, 2/19/09)

53063-0017; 240855; "[Triazole-^{14}C]WL136184 (KNF-S-474c): The Isolation and Identification of Metabolites Following a Single Oral Dose (200 mg kg^{-1}) to the Rat"; (K.A. Richardson; Sittingbourne Research Centre, Sittingbourne,, Kent ME9 8AG, England; Report No. SBGR.90.108; 1/29/91); The urine and feces recovered from male Fischer 344 rats dosed orally with 200 mg/kg of [Triazole-^{14}C]WL136184 (KNF-S-474c) (cis-isomer of metconazole) were analyzed for the presence of metabolites. Thin layer chromatography, high pressure liquid chromatographic, mass spectrographic and nuclear magnetic resonance analytical techniques were used to isolate and identify the metabolites. The metabolites which were identified constituted 53% of the administered dose. The fecal metabolites were hydroxylated moieties of the parent compound. Two of the metabolites were further oxidized to the carboxylate. The one urinary metabolite which was identified was 1,2,4-triazole. **Supplemental study.** (Moore, 2/19/09)

53063-0017; 240856; "The Excretion of ^{14}C- WL 136184 in Bile-Duct Cannulated Rats"; (D.R. Hawkins, L.F. Elsom, T.J. Kane; The Department of Chemical Metabolism and Radiosynthesis, Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Report No. HRC/SLL 204/91719; 10/1/91); Three bile-duct cannulated Fischer 344 rats/sex were dosed orally by gavage with 2 mg/kg of ^{14}C- WL136184 (cis-isomer of metconazole) (batch no. S.1190/2, specific activity: 44.3 uCi/mg, radiochemical purity: 98.2%). Unlabeled WL 136184 (batch no. 002/90; purity not reported) was used to adjust the specific activity of the dosing preparation.

Bile, urine and feces were collected up to 48 hours post-dose. The primary site of radiolabel recovery was in the bile; 79 and 83% of the administered dose for the males and females, respectively. Total recovery of the radiolabel in the bile, urine, and carcass indicate that 87 to 97% of the administered dose was absorbed. **Supplemental study.** (Moore, 2/23/09)

53063-0042; 245730; "[Cyclopentyl-^{14}C] WL148271 (KNF-S-474m): The Fate of a Single High Oral Dose of 164 Mg Per Kg in the Fischer 344 Rat; (B.J. Morrison, K.A. Richardson; Sittingbourne Research Centre, Sittingbourne, Kent ME9 8AG, England; Report No. SBGR.91.188; 3/5/92); Five Fischer 344 rats/sex were dosed orally by gavage with 164 mg/kg of [Cyclopentyl-^{14}C]WL148271 (KNF-S-474m (batch no. S1164/1, specific radioactivity: 1.51 uCi/mg, radiochemical purity: 99.9%, cis:trans ratio: 79:21, chemical purity: > 99%). . Urine and fecal samples were collected up to 5 days post-dose. The distribution of radiolabeling in specific tissues/organs was assayed at that time. The predominant route of excretion was via the feces. Eighty one and 65% of the administered dose was excreted in the feces for the males and females, respectively. Fourteen and 28% of the dose was recovered in the urine of the males and females, respectively. Fifteen and 19% of the dose was recovered in the 1st 24 hours post-dose for the males and females, respectively. The gastrointestinal tract was the organ with the highest concentration of the radiolabel. The adrenal glands and liver were the other two sites with higher levels of radioactivity. High pressure liquid chromatographic techniques were used to isolate and identify the metabolites in the urine and feces. The metabolites which were isolated and identified were hydroxylated moieties of the parent compound. Two of the eight metabolites were further oxidized to the carboxylate. The identified moieties comprised 55 and 43% of the administered dose for the males and females, respectively. **Study supplemental.** (Moore, 5/6/09)

SUBCHRONIC STUDIES

Rat 2-Week Neurotoxicity Study

53063-0009; 239050; "KNF-474m:Preliminary Neurotoxicity Study by Dietary Administration to CD Rats for 2 Weeks"; (S. Cooper; Huntingdon Life Sciences Ltd., Alconbury, Huntingdon, Cambridgeshire, PE28 4HS, England; Project ID. No. KRA 065/ 020005; 8/8/02); Ten Crl:CD (SD)IGS BR rats/sex/group received 0, 100, 540 or 3000 ppm of KNF-474m (lot no. 9Z521; purity: 98.99%) in the diet for 2 weeks ((M) 0, 11.0, 59.6, 216.8 mg/kg/day, (F) 0, 10.6, 52.8, 206.1 mg/kg/day). No deaths resulted from the treatment. Both sexes in the 3000 ppm group lost weight over the two week period. The mean body weight gain of the 540 ppm males was less than that of the control group ($p<0.05$). The mean food consumption of both sexes in the 3000 ppm group was less than the control group over the course of the study. No treatment-related effects were apparent in the FOB and motor activity assessments. In the necropsy examination, the livers of both sexes in the 3000 ppm group were enlarged ((M) 0: 0/5 vs. 3000: 5/5, (F) 0:0/5 vs. 3000: 4/5). The prostate and seminal vesicles of the 3000 ppm males were small (0: 0/5 vs. 3000: 4/5). The uteri of the 3000 ppm females were thin (0: 0/5 vs. 3000: 4/5). **No adverse effect indicated. NOEL:** Not established (study was not sufficiently rigorous to select a NOEL); **Study supplemental.** (Moore, 2/13/09)

Rat 4-Week Neurotoxicity Study

53063-0009; 239049; "KNF-474m: Neurotoxicity Study by Dietary Administration to CD Rats for 4 Weeks"; (S. Cooper; Huntingdon Life Sciences Ltd., Alconbury, Huntingdon, Cambridgeshire, PE28 4HS, England; Project ID. No. KRA/068 022386; 9/30/02); Ten Crl:CD (SD)IGS BR rats/sex/group received 0, 50, 170 or 500 ppm of KNF-474m (lot no. 9Z521; purity: 98.99%) in the diet for 4 weeks ((M) 0, 4.84, 15.7, 47.1 mg/kg/day, (F) 0, 5.10, 17.6, 49.8 mg/kg/day). No deaths resulted from the treatment. The body weight gain and food consumption of the 500 ppm females were less than the control values over the course of the study (NS). No treatment-related effects were noted in the FOB or motor activity assessments. The necropsy and histopathological evaluations did not reveal any treatment-related effects. **No adverse effect indicated. Rat 4-Week Neurotoxicity NOEL:** (M/F) 500 ppm ((M) 47.1 mg/kg/day, (F) 49.8 mg/kg/day) (based upon the lack of treatment-related neurotoxic effects for the both sexes in the 500 ppm treatment

group); **Study supplemental** (the study was not performed in accordance with a standard guideline protocol). (Moore, 2/13/09)

Rat 14-Day Repeated Dosing Dermal Toxicity Study

53063-0007; 239038; "A 14-Day Range-Finding Dermal Toxicity Study in Fischer 344 Rats with Metconazole Technical"; (K.L. Bonnette; Charles River Laboratories, Inc., Discovery and Development Services, Ohio Division, Spencerville, OH; Project ID. ODV00035; 1/31/06); The skin of 5 Fischer 344 rats/sex/group was exposed to 0, 250, 500 or 1000 mg/kg/day of Metconazole technical (lot no. AS 2122a; purity: 98.7% (84.3% cis, 14.4% trans)) 6 hours/day for 14 consecutive days. Reverse osmosis distilled water was used to moisten the test material. No deaths resulted from the treatment. The mean body weights and food consumption were not affected by the treatment. No treatment-related clinical signs were noted in the functional observational battery. No treatment-related effects were apparent in the clinical chemistry evaluation. No treatment-related lesions were noted in the necropsy examination. **No adverse effect indicated. 14-Day repeated dosing dermal toxicity NOEL:** (M/F) 1000 mg/kg/day (based upon the lack of treatment-related effects at the 1000 mg/kg/day treatment level). **Study supplemental** (non-guideline study). (Moore, 12/8/08)

Rat 21-Day Repeated Dosing Dermal Toxicity Study

** 53063-0007; 239039; "Metconazole (KNF-S-474m): A 21-Day Dermal Toxicity Study in Fischer 344 Rats"; (K.L. Bonnette; Charles River Laboratories, Inc., Preclinical Services, Spencerville, OH; Project ID. VP-28361; 3/17/06); The skin of 10 Fischer 344 rats/sex/group was exposed to 0, 250, 500 or 1000 mg/kg/day of Metconazole technical (lot no. AS 2122a; purity: 98.7% (84.3% cis, 14.4% trans)) 6 hours/day for 21 consecutive days. Reverse osmosis distilled water was used to moisten the test material. The mean body weights and food consumption were not affected by the treatment. The hematology evaluation and ophthalmology examination did not reveal any apparent treatment-related effects. In the clinical chemistry evaluation, the mean glucose levels were elevated for both sexes in the 1000 mg/kg group and for the males in the 500 mg/kg group ($p<0.01$or 0.05). The mean serum albumin concentrations of the 500 and 1000 mg/kg females were less than the control value ($p<0.01$). The mean absolute and relative liver weights of the 500 and 1000 mg/kg females and the mean relative liver weight of the 1000 mg/kg males were greater than the control values ($p<0.01$ or 0.05). The mean absolute and relative thymus weights of the 500 and 1000 mg/kg males were less than the control values ($p<0.05$). The histopathological examination did not reveal any treatment-related lesions. **No adverse effect indicated. 21-Day Repeated Dosing Systemic Dermal Toxicity NOEL:** (M/F) 250 mg/kg/day (based upon the increased glucose levels noted for the males and the decreased serum albumin level and increased absolute and relative liver weights for the females in the 500 mg/kg group); **Dermal Irritation NOEL:** (M/F) 1000 mg/kg/day (based upon the lack of irritation at the highest dose level); **Study acceptable.** (Moore, 12/8/08)

Dog Oral Toxicity Dose Range-Finding Study

53063-0006; 239037; " WL 148271: Oral (Capsule) Maximum Tolerated Single Dose Study in the Beagle"; (N. Pickersgill; Hazleton UK, Harrogate, North Yorkshire, HG3 1PY, England; Project ID. 579/21; 7/31/91); One beagle dog/sex was dosed orally by capsule with 0, 300 or 400 mg/kg of WL148271 (lot no. 89-01; purity: 95.3%). No deaths resulted from the treatment. Emesis was found in the cages of both animals treated with 400 mg/kg within 4 hours of dosing and in the cage of the female in the 300 mg/kg group within 5 hours of dosing. The body weights of the animals in the two treated groups decreased over the 1st 24 hours post-dose. The food consumption of the animals in the 400 mg/kg group during this post-dose period was less than the level recorded prior to dosing. Food consumption recovered for all of the treated animals by day 4. In the necropsy examination, the gastrointestinal tract of both animals in the 400 mg/kg demonstrated possible treatment-related lesions (red area in the duodenum of the male and raised areas within the jejunum of the female). **No adverse effect indicated. Study supplemental.** (Moore, 12/5/08)

Dog Subchronic Dietary Toxicity Study

**** 53063-0043; 245731**; "WL148271: 90 Day Oral (Dietary Administration) Toxicity Study in Dogs"; (N. Pickersgill; G. Ince; Hazleton UK, Harrogate, North Yorkshire, England, HG3 IPY; Report No. 6396-579/23; 9/3/91); Five beagle dogs/sex/group received 0, 60, 600 or 6000 ppm of WL148271 (KNF-S-474m) (batch no. 89-01; purity: 95.3%) for 13 weeks in the diet ((M) 0, 2.47, 24.4, 225.0 mg/kg/day, (F) 0, 2.60, 24.2, 205.9 mg/kg/kg (calculated by the reviewer)). The mean body weight gain of both sexes in the 6000 ppm group and the females in the 600 ppm group were less than that of the control animals (NS, p<0.01 or 0.001). The mean food consumption of both sexes in the 6000 ppm group and the females in the 600 ppm group was less than the control values (p<0.05 or 0.001). In the ophthalmological examination, all of the animals in the 6000 ppm group suffered from lenticular degeneration (cataracts). In the hematology examination, the mean hemoglobin concentration, red blood cell count and hematocrit of both sexes in the 6000 ppm group during the 13th week of the treatment were less than the control values (p<0.05 or 0.01). In the clinical chemistry evaluation, the serum alkaline phosphatase activity levels of both sexes in the 6000 ppm group were greater in than that of the control group at 6 and 13 weeks of treatment (p<0.01). The gamma glutamyl transpeptidase activity level of the 6000 ppm males was greater than that of the control group at 6 and 13 weeks of treatment (p<0.01). The serum albumin levels of both sexes in the 6000 ppm were less than the control values at 6 and 13 weeks of treatment (p<0.05, 0.01 or 0.001). In the necropsy examination, the mean relative liver weights of both sexes in the 6000 ppm group were elevated in comparison to the control group (NS, p<0.05). The mean relative spleen and thyroid weights of the 6000 ppm females were greater than the control group values (p<0.05 or 0.001). In the histopathological examination, hepatocytic hypertrophy was noted in the livers of both sexes in the 6000 ppm ((M) 0: 0/5 vs. 6000: 5/5, (F) 0: 0/5 vs. 6000: 5/5). Hematopoiesis were evident in the spleen of both sexes in the 6000 ppm group ((M) 0: 0/5 vs. 6000: 5/5, (F) 0: 0/5 vs. 6000: 5/5). Involution of the thymus was noted for the 6000 ppm males ((M) 0: 0/5 vs. 6000: 3/5). An increased incidence of tubular vacuolation was evident in the kidneys of the 6000 ppm females (0: 1/5 vs. 6000: 4/5). **Possible adverse effect:** lenticular degeneration (cataracts). **Dog Subchronic Dietary Toxicity NOEL: (M)** 600 ppm (24.4 mg/kg/day) (based upon treatment-related effects upon the body weight gain, food consumption, hematology, clinical chemistry and histopathological lesions in the 6000 ppm group) **(F)** 60 ppm (2.60 mg/kg/day) (based upon lower body weight gain and food consumption for the 600 ppm group); **Study acceptable.** (Moore, 5/7/09)

MECHANISTIC STUDIES

53063-0008; 239047; "A Measurement Study of Serum Steroid Hormone Concentrations and Hepatic Drug-Metabolizing Enzyme Contents during Late Gestation in Rats Fed Diets Containing KNF-474m"; (S. Teramoto; The Institute of Environmental Toxicology, Mitsukaido-shi, Ibaraki 303-0043, Japan; Project ID. IET 02-0058; 10/8/02); Twenty four female Crj:CD (SD)[IGS] rats/group received 0, 30, 150 or 750 ppm of KNF-474m (lot no. 9Z521; purity: 98.99%) in the diet for 3 weeks prior to mating, during mating, and up to day 19 or 21 of gestation (0, 1.82, 8.89, 43.0 mg/kg/day). (Note: 50% of the dams in each group were euthanized on either day 19 or day 21). The mean body weight gain of the 750 ppm dams during the premating and gestation period was less than that of the control group (p<0.01). The mean food consumption of the 750 ppm dams was less than the control group's consumption during the 1st week of premating and during the gestation period (p<0.01 or 0.05). The mean number of corpora lutea, implantation sites and no. of live fetuses per litter were less than the control values (p<0.01 or 0.05). The mean number of resorptions of the 750 ppm dams was greater than the control group value. The serum levels of 17β-estradiol of the 750 ppm dams on days 19 and 21 were less than those of the control group (p<0.01, NS). The progesterone levels on days 19 and 21 were not significantly affected by the treatment. The estradiol/progesterone ratios for the 750 dams on days 19 and 21 were less than those of the control group (p<0.05 or 0.01). The absolute and relative liver weights of the 750 ppm dams on day 21 were greater than the control values (p<0.01). No effect on liver weight was apparent on day 19. Microsomal protein in the liver was elevated for both the dams in the 150 and 750 ppm groups on day 19, but not on day 21 (p<0.01). The cytochrome P-450 content in the livers of the 150 and 750 ppm dams was elevated on day 21, but not on day 19 (p<0.05 or 0.01). Hepatic cytochrome P-450 isozymes were assayed. CYP 2B1 levels were elevated for all of the treated groups in comparison to the control on day 19 (p<0.01). Only the 750 ppm dams

had higher levels than the control group on day 21 (p<0.01). The isozyme CYP 3A2 level of the 750 ppm dams was elevated on both days 19 and 21 (p<0.01). Isozyme CYP 4A1 levels did not demonstrate any consistent treatment-related effect on either day 19 or 21. In the evaluation of proliferating cell nuclear antigen (PCNA)-positive ovarian cells on day 21 of gestation, a greater percentage of corpora lutea in the ovaries of the 750 ppm dams had at least one lutein cell which was positive for PCNA (0: 23/49 (47%) vs. 750: 28/35 (80%)). Administration of the test material at a rate of 43.0 mg/kg/day resulted in the reduced levels of 17β-estradiol in the serum by day 21 of gestation and a lower estradiol to progesterone ratio on day 21. This observation coincided with the altered profile of cytochrome P-450 isozymes in the liver of these animals. The increased levels of isozyme CYP 3A2 likely facilitated an increased metabolism of the estradiol, thus reducing the serum level. The author of the report surmised that the lower estradiol to progesterone ratio likely affected parturition and resulted in the maternal deaths which were noted in the two-generation reproduction study. **Study supplemental.** (Moore, 2/11/09)

53063-0017; 240857; "Study to Investigate the Effects of WL 136184 on Rat and Mouse Hepatic Xenobiotic Metabolising Enzymes"; (N.R. Worrell; BIBRA Toxicology International, Carshalton, Surrey, SM5 4DS, UK; Report No. 980/2/91; 6/21/91); Eight Fischer 344 male rats/group received 0 or 1000 ppm of WL 136184 (KNF-S-474 cis-isomer) (batch no. 12, purity: 94.2%) in the diet for 7 or 28 days (7 days: 102.7 mg/kg/day, 28 days: 86.7 mg/kg/day). Eight CD-1 male mice/group received 0 or 300 ppm of the test material for 7 or 28 days in the diet (7 days: 62.5 mg/kg/day, 28 days: 58.3 mg/kg/day). A positive control group of 8 animals/group of both rats and mice received 500 ppm of phenobarbitone in the diet for 28 days (rat: 43.9 mg/kg/day, mouse: 93.6 mg/kg/day). No deaths occurred during the study. The mean body weight of the WL 136184-treated rats was less than that of the control group over the course of the 4-week treatment period (NS). The mean body weight of the WL 136184-treated mice was not affected by the treatment. The mean body weights of the phenobarbitone-treated rats and mice were greater than the control values (p<0.05 or NS). The mean food consumption of the WL 136184-treated rats was less than that of the control group (NS). The absolute and relative liver weights of the phenobarbitone-treated rats and mice and the 7-day WL 136184-treated mice and the mean relative liver weights of the 7- and 28-day WL 136184-treated rats and the 28-day WL 136184-treated mice were greater than the control values (p<0.05, 0.01 or 0.001). Biochemical analysis of the liver tissue demonstrated increased microsomal protein for both the 7- and 28-day WL 136184-treated rats and mice and the 28-day phenobarbitone-treated rats and mice (p<0.05, 0.01 or 0.001). The microsomal cytochrome P-450 levels in the livers of the both the 7- and 28-day WL 136184-treated rats and mice and the 28-day phenobarbitone-treated rats and mice were greater than the control values (p<0.001). The ethylmorphine N-demethylase and the 7-ethoxycoumarin O-deethylase activity levels of both the 7- and 28-day WL 136184-treated rats and mice and the 28-day phenobarbitone-treated rats and mice were greater than the control activities (p<0.01 or 0.001). The induction of 7-ethoxyresorufin O-deethylase and lauric acid 11-hydrolase enzymes was less for the WL 136184-treated rats and mice (NS or p<0.05) than was evident for the phenobarbitone-treated animals (p<0.001). Overall, WL 136184 demonstrated a potential to induce microsomal cytochrome P-450 with a metabolic profile similar to that of phenobarbitone. The hepatocytes in the livers of the 28-day WL-136184-treated rats and mice demonstrated slight to marked vacuolation. The livers of the phenobarbitone-treated rats and mice exhibited hepatic hypertrophy. **Supplemental study.** (Moore, 2/24/09)

DERMAL PENETRATION STUDIES

53063-0009; 239052; "Metabolism of KNF-474m in Rats"; (E. Yamamoto; The Institute of Environmental Toxicology, Mitsukaido-shi, Ibarakii, 303-0043, Japan; Project ID. IET01-8002; 8/16/02); In this study, the pharmacokinetics and tissue distribution of metconazole was evaluated. In the pharmacokinetic phase, three Fisher 344/DuCrj rats/sex/group were dosed orally by gavage with 2 or 200 mg/kg of [Cyclopentyl-^{14}C]KNF-474 (lot no. CP-2397, specific activity: 1.83 GBq/mmol, radiochemical purity: 98.8% (cis/trans isomeric ratio: 85/15)). The specific activity of the dosing preparations was adjusted by using unlabeled KNF-474m (lot no. 9Z521, purity: 98.99% (cis/trans isomeric ratio: 83/16)) in the preparations. Blood samples were drawn from an in-dwelling catheter up to 72 hours post-dose for the 2 mg/kg group and up to 120

hours post-dose for the 200 mg/kg group. In the tissue distribution study, 9 rats/sex were treated with a single dose of 2 mg/kg (Group A), 12 animals/sex were treated with a single dose of 200 mg/kg (Group B) and 6 animals/sex were treated for 14 days with 2 mg/kg/day of the radiolabeled test material (Group C). For Group A, 3 animals/sex/time point were euthanized at 0.5, 24 and 72 hours post-dose. For Group B, 3 animals/sex/time point were euthanized at 4, 24, 72 and 120 hours post-dose. For Group C, 3 animals/sex/time point were euthanized at 0.5 and 72 hours post-final dose. In the pharmacokinetic study, the time to peak plasma levels was 0.25 and 4 hours post-dose for the 2 and 200 mg/kg treatment groups, respectively. The biological half-lives for the β elimination phase were 20 and 34 hours for the males and females, respectively, in the 2 mg/kg group and 25 and 34 hours for the males and females, respectively, in the 200 mg/kg group. The liver was the organ in which the greatest percentage of the administered dose was recovered. The liver and the adrenal gland had the highest concentrations of the radiolabel for the 2 and 200 mg/kg treatment groups. For the 200 mg/kg treatment group, the concentrations of radiolabel in the kidneys, thyroid gland, skin and hair, and adipose tissue were also relatively high over the 120-hour assay period. The concentrations of radiolabel in the brain, heart, pituitary gland, lung, prostate, seminal vesicles and testes of this group were high during the first 24 to 72 hours post-dose but the levels had appreciatively diminished by 120 hours. At the conclusion of the 14-day treatment regimen of 2 mg/kg/day, the concentrations of radiolabel in the liver and adrenal glands were the highest among the assayed tissues. Multiple dosing resulted in greater residual concentrations of the radiolabel in each of the assayed tissues/organs. The biological half-lives of the radiolabel in the liver, kidneys, adipose tissue, and plasma ranged between 14 and 43 hours for the three different dosing regimens. The biological half-life for the radiolabel in the adrenal gland of the males in both groups A and C were greater than that range. The biological half-live in the erythrocytes of the Group C males and females was extended to 90 and 79 hours, respectively. **Supplemental Study.** (Moore, 3/2/09)

53063-0009; 239053, 239054; "KNF-S1474m (WL 148271): A Study of Absorption and Excretion following Percutaneous Administration to the Rat"; (K. Cornelissen; Hazleton UK, Harrogate, North Yorkshire, HG3 1PY, England; Project ID. 579/47; 12/27/90); The skin of 4 Fischer 344 female rats/group was exposed to 2.5 mg/animal of (Cyclopentanol-1-^{14}C)-WL148271 (batch no. S1116, radiochemical purity: 99.0%, specific activity: 31.09 uCi/mg, chemical purity: 99.0%, (81:19 cis:trans) for 0 or 4 hours (Groups B and C). Another cohort of 12 females were exposed in the same manner for 8 hours and 4 animals/time point were euthanized at the end of the exposure (Group D), at 24 hours post-application (Group E) and at 72 hours post-application (Group F). Group A consisted of 4 control animals which were treated in the same manner at the treated animals except they were not exposed to the test material and were euthanized at 24 hours post-study initiation. The specific activity of the dosing preparation was adjusted using unlabeled WL-148271 (batch no. ST 89/008, purity: 95 to 96%.). Recovery of radioactivity was primarily in the washes of the application site (81 to 91% of administered dose) and in the treated skin (4.5 to 15.4% of the administered dose). The percentage of the administered dose which was systemically absorbed increased from 1.1% during the first 4 hours of exposure to 1.7% after 8 hours and to 7.6% after 8 hours of exposure and an additional 64 hours interval post-exposure. The urine was the predominate route of excretion through 24 hours. By 72 hours, recovery of radiolabel in the feces exceeded that of the urine. The cutaneous absorption rate of radioactivity was greatest during the first 4-hour interval with a value of 0.86 ug equivalents of WL-148271/cm^2 of skin/hour, declining slightly for the 0 to 8-hour interval to 0.66 ug equivalents of WL-148271/cm^2 of skin/hour and to 0.32 ug equivalents of WL-148271/cm^2 of skin/hour for the 0 to 72-hour interval. The adrenal gland had the highest concentration of radiolabel throughout the 72 hour study period. The concentration in the adrenals ranged from 5 to 11 times that of the carcass over the course of the study. Likewise, the concentration in the adrenals exceeded that of the blood by a factor of 41 to 89 times. **Study supplemental** (study was not performed according to guideline requirements)**.** (Moore, 3/11/09)

53063-0013; 241023; "WL 136184 (KNF-S-474C): A Study of Absorption and Excretion following Dermal Application to the Rat"; (E.J. Little; Hazleton UK, Harrogate, North Yorkshire, England; Report No. 6915-579/93; 2/6/92); The skin of 4 Fischer 344 female rats/group was

exposed to 1.5 mg/animal of (^{14}C-Cyclopentyl)-WL136184 (batch no. 001/91, radiochemical purity: 99.0%, specific activity: 37.74 uCi/mg, chemical purity: 99.0%) for 0 or 4 hours (Groups B and C). Another cohort of 12 females were exposed in the same manner for 8 hours and 4 animals/time point were euthanized at the end of the exposure (Group D), at 24 hours post-application (Group E) and at 72 hours post-application (Group F). Group A consisted of 4 control animals which were treated in the same manner as the treated animals except they were not exposed to the test material and were euthanized at 24 hours post-study initiation. The specific activity of the dosing preparation was adjusted using unlabeled WL-136184 (batch no. 002/90, purity: 99.3%). Recovery of radioactivity was primarily in the washes of the application site (65 to 83% of administered dose) and on the nylon gauze covering (7 to 27% of the administered dose). The percentage of the administered dose which was systemically absorbed increased from 0.7% after 4 hours of exposure to 0.9% after 8 hours and to 1.8% after 8 hours of exposure and an additional 64 hours interval post-exposure. Excretion of the radiolabel was greater via the feces than the urine over the course of the 72-hour sample collection period. The cutaneous absorption rate of radioactivity was greatest during the initial 4-hour interval with a value of 0.21 ug equivalents of WL-148271/cm^2 of skin/hour, declining to 0.13 ug equivalents of WL-148271/cm^2 of skin/hour for the 0 to 8-hour post-application interval and to 0.03 ug equivalents of WL-148271/cm^2 of skin/hour for the 0 to 72-hour interval. The adrenal gland had the highest concentration of radiolabel throughout the 72 hour study period. The concentration in the adrenals ranged from 10 to 24 times that of the carcass over the course of the study. Likewise, the concentration in the adrenals exceeded that of the plasma by a factor of 100 to 295 times. **Study supplemental** (study was not performed according to guideline requirements)**.** (Moore, 3/12/09)