CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Tetraconazole

Chemical Code # 5939, **Tolerance** # 53004
SB 950 # NA

7/12/07

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect indicated.
Chronic toxicity, dog:	No 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, no adverse effect indicated.
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 studies submitted nor required at this time.

Toxicology one-liners are attached.

All record numbers through 223929 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T071207
Revised by T. Moore, 7/12/07

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

COMBINED, RAT

** 53004-0009; 223910; "M 14360: Potential Tumorigenic Effects and Toxic Effects in Prolonged Dietary Administration to Rats"; (S.J. Crome, *et. al.*; Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Study No. AGR 74/911683; 11/11/92); Fifty Crl:CD (SD) rats/sex/group received 0, 10, 80 or 640 ppm of M 14360 Technical (batch no. FCF/T/72; purity: 94.6%) in the diet for up to 104 weeks. An additional 50 male rats received 1280 ppm in the diet for the same time period ((M) 0, 0.4, 3.4, 27.7 and 59 mg/kg/day, (F) 0, 0.6, 4.4, and 39.4 mg/kg/day). These animals were designated as part of the oncogenicity phase. An additional 20 animals/sex/group received the same treatments for 52 weeks. These animals were part of the toxicity phase of the study. Survival of the animals was not affected by the treatment. The mean body weight gain of the males in the 1280 ppm group and of both sexes in the 640 ppm group was less than that of controls over the course of the study ($p<0.05$ or 0.01). The ophthalmology examination and urinalysis did not reveal any treatment-related effect. Although some of the parameters for the treated groups in the hematological evaluation were statistically lower than those of the control, any apparent effects were not physiologically relevant. In the clinical chemistry evaluation, the serum cholesterol levels were elevated for the females in the 640 ppm group at various times during the study. The inorganic phosphate levels was elevated in the serum of the 1280 ppm males throughout the study and for the 640 ppm males at 52 and 78 weeks of treatment ($p<0.05$ or 0.01). However, the effect was not consistent throughout the study. In the necropsy examination, the mean liver weights of the males in the 1280 ppm group and the females in the 640 ppm group were greater than the control values after 52 weeks of treatment and were greater for the males in the 1280 ppm group and both sexes in the 640 ppm group after 104 weeks of treatment ($p<0.01$). The mean kidney weights for the males in the 1280 ppm group and the females in the 640 ppm group were greater than those of the controls after both 52 and 104 weeks of treatment ($p<0.01$). In the histology examination, centrilobular hepatocyte enlargement was noted in the liver of both sexes in the 640 ppm group and the males in the 1280 ppm group after 52 weeks of treatment and in the livers of both sexes in the 80 and 640 ppm groups and the 1280 ppm group after 104 weeks. Fine vacuolation of the centrilobular and midzonal hepatocytes was noted in the livers of the males in the 640 and 1280 ppm group after both 52 and 104 weeks of treatment. An increased incidence and severity of fat inclusions were noted in the centrilobular and midzonal hepatocytes of the males in the 640 and 1280 ppm groups after 52 and 104 weeks of treatment. An increased incidence of bile duct hyperplasia was noted in the livers of the 1280 ppm males and 640 ppm females after 104 weeks of treatment. Other apparent treatment-related effects included pyelitis in the kidneys of the 1280 ppm males after 52 weeks of treatment, squamous cell metaplasia in the uterus of the 640 ppm females after 52 weeks of treatement and minimal follicular epithelial cell hypertrophy in the thyroid of the 1280 ppm males and dorsal/dorso-lateral compression of the brain and osseous hypertrophy of the cranium and parietal bone of the males in the 640 and 1280 ppm groups. **No adverse effect indicated. Rat Chronic Dietary Toxicity NOEL:** 10 ppm ((M) 0.4 mg/kg/day, (F) 0.6 mg/kg/day) (based upon the enlargement of the centrilobular hepatocytes in the livers of both sexes in the 80 ppm treatment group); **no evidence of oncogenic potential; Study acceptable.** (Moore, 3/30/07)

CHRONIC TOXICITY, RAT

See Combined, Rat above.

CHRONIC TOXICITY, DOG

** 53004-0007; 223906; "M 14360 Dietary Toxicity Study in Beagle Dogs (final report - repeated daily dosage for 52 weeks); (A. Makin, *et. al.*; Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Study No. AGR 72-G/901546; 1/22/91); Four beagle dogs/sex/group received 0, 22.5, 90 or 360 ppm of M 14360 Technical (batch no. FCF/T/72; purity: 94.6%) in the diet for 12 months ((M) 0, 0.73, 2.95, 12.97 mg/kg/day; (F) 0, 0.82, 3.33, 14.50 mg/kg/day). No deaths resulted from the treatment. Although all of the study groups

experienced weight loss or minimal weight gain over the course of the study, the 360 ppm group lost the most weight. There was no apparent treatment-related effect on food consumption during the study. In the hematology evaluation, the activated thromboplastin time of both sexes in the 360 ppm group was increased at the various time points over the course of the study ($p<0.01$ or 0.05). In the clinical chemistry evaluation, the serum alkaline phosphatase activities were increased for both sexes in the 360 ppm group over the course of the study ($p<0.01$). The serum GPT and OCT activities and the serum cholesterol concentration of both sexes in the 360 ppm group were elevated above the control values throughout much of the treatment period ($p<0.01$, 0.05 or NS). The serum phosphorus levels were elevated for both sexes in the 360 ppm group over the course of the study ($p<0.01$). No apparent treatment-related effect was noted in either the urinalysis or ophthalmology examinations. The mean liver and kidney weights of both sexes in the 360 ppm group were greater than the control values ($p<0.01$). The apparent enlargement of hepatocytes, eosinophilic inclusions in the hepatocytes and hepatocytic rarefaction were noted in the livers of the 360 ppm animals. Cortical tubular hypertrophy was noted in the kidneys of the 360 ppm animals. A few apoptotic bodies were observed in the cortical tubules of these animals as well. **No adverse effects were evident. Dog Chronic Dietary NOEL:** (M/F) 90 ppm ((M) 2.95 mg/kg/day, (F) 3.33 mg/kg/day) (based upon the increased activity of alkaline phosphatase in the serum, the increased liver and kidney weights, the incidence of enlarged hepatocytes in the liver and of tubular lesions in the kidneys of both sexes in the 360 ppm treatment group); **Study acceptable.** (Moore, 3/22/07)

ONCOGENICITY, RAT

See Combined, Rat above.

ONCOGENICITY, MOUSE

**** 53004-0008; 223909**; "M 14360: Potential Tumorigenic Effects in Prolonged Dietary Administration to Mice"; (S.J. Crome, *et. al.*; Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Study No. AGR 73/920469; 12/10/92); Fifty Crl: CD-1 (ICR) mice/sex/group received 0, 10, 90, 800 or 1250 ppm of M 14360 Technical (batch no. FCF/T/80-89; purity: 95.05%) in the diet for 80 weeks ((M) 0, 1.4, 12.0, 118, 217 mg/kg/day, (F) 0, 1.6, 14.8, 140, 224 mg/kg/day). The survival of both sexes in the 1250 ppm group was significantly reduced. The mean body weight gain for both sexes in the 800 and 1250 ppm groups was less than that of the control group during the study ($p<0.05$ or 0.01). The mean food consumption was not apparently affected by the treatment. The differential white blood cell count and morphology assessments did not reveal any treatment-related effects. The mean liver weights of both sexes in the 90, 800 and 1250 ppm groups were greater than those of the control ($p<0.05$ or 0.01). The mean kidney weights of both sexes in the 800 and 1250 ppm groups and the males in the 90 ppm group were greater than control values, as well ($p<0.05$ or 0.01). In the histopathological evaluation, there was an increased incidence of both benign and malignant tumors in the livers of both sexes in the 800 and 1250 ppm groups. An increased incidence of generalized hepatocytic enlargement and vacuolation and granulomatous inflammation were evident in the livers of both sexes in the 800 and 1250 ppm. Bile duct hyperplasia was noted in the livers of both sexes in the 1250 ppm group and the males in the 800 ppm group. An increased incidence of generalized fat deposition in the hepatocytes was noted in the livers of the males in the 90, 800 and 1250 ppm groups. Eosinophilic and basophilic hepatocytes were evident in the livers of the females in the 800 and 1250 ppm groups. Pigmented macrophages were present in a greater number of livers of both sexes in the 800 and 1250 ppm groups. An increased incidence and/or severity of cortical scarring with atrophic tubules were noted in the kidneys of both sexes in the 1250 ppm group and the females in the 800 ppm group. Papillitis was noted in the kidneys of the 1250 ppm males. Spermatozoa were not present in some of the epididymides of the 90, 800 and 1250 ppm males. Tubular atrophy of the testes was noted for some of the males in the 1250 ppm group. Reduced spermatogenesis in the testes was evident for males in the 800 and 1250 ppm groups. Thickening of the cranial bone was noted for both sexes in the 800 and 1250 ppm groups. **Possible adverse effect:** increased incidence of malignant and benign liver tumors, reduced spermatogenesis in the testes. **Chronic Dietary NOEL:** (M/F) 10 ppm ((M) 1.4 mg/kg/day, (F) 1.6 mg/kg/day) (based upon the increased mean liver weights of both sexes in the 90 ppm group

and the lack of spermatozoa in the epididymides of some of the males in the 90 ppm group); **carcinogeneity was noted**; **Study acceptable.** (Moore, 3/27/07)

REPRODUCTION, RAT

** 53004-0006; 223904; "A Study of the Effect of M 14360 (Technical) on Reproduction Function of Two Generations in the Rat"; (P.R. Ryle, R.E. Masters, J.M. Offer, I.S. Dawe, A. Anderson; Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Report No.AGR 46/9076; 2/18/91); Twenty-eight Crl:CD® (SD) rats/sex/group (F0 Generation) received 0, 10, 70 or 490 ppm of M 14360 Technical (batch no. FCF/T/72; purity: 94.6%) in the diet for 10 weeks prior to mating, mating, 3 weeks of gestation and 3 weeks of lactation. At that time 28 F1A animals/sex/group were selected as parents and treated for an additional 10 weeks, followed by mating and 3 weeks each for gestation and lactation of the F2 generation. The F0 animals were remated after a 10-day interlude and treatment continued through the 3-week gestation and lactation periods (F1B Generation). Eight females in the 490 ppm group, six from the F0 Generation and two from the F1A Generation were euthanized or found dead during the study. The deaths of seven of these animals occurred at or near the time of their expected parturition. The mean body weight gains of the 490 ppm females in the F0 generation and of both sexes in the 490 ppm group of the F1A generation were less than the respective control values during the premating period ($p<0.01$ or 0.05). The mean absolute and/or relative liver weights of the 490 ppm adult animals in both generations were greater than those of the control ($p<0.01$). The incidence of minimal centrilobular hepatocytic enlargement was noted in the livers of both sexes in the 490 ppm group of both generations. Although the mean absolute and/or relative kidney weights of the 490 ppm group of both generations were greater than those of the control ($p<0.01$), no treatment-related histological lesions were evident in the kidneys of these animals. The mating parameters of either generation were not apparently affected by the treatment. The mean litter sizes (day 0) of the 490 ppm group in both F0 generation matings and the F1A generation mating were less than those of the control ($p<0.01$ or NS). The mean pup weights of the 490 ppm treatment group for all three matings were less than those of the control from day 8 *post-partum* through the end of the lactation period ($p<0.01$ or 0.05). The developmental landmarks of vaginal opening and balanopreputial cleavage were delayed for the F1A offspring. The mean relative liver weights for the weanlings of all three matings were greater than those of the controls ($p<0.01$). **No adverse effect indicated. Parental NOEL: (M/F)** 70 ppm ((M) 5.3 mg/kg/day, (F) 5.9 mg/kg/day) (based upon histological effects on the liver and reduced body weight gain of the adults in the 490 ppm group of both generations); **Reproductive NOEL:** 70 ppm (5.9 mg/kg/day) (based upon the reduced litter size of the 490 ppm group in all three matings); **Developmental NOEL:** 70 ppm ((M) 5.3 mg/kg/day, (F) 5.9 mg/kg/day) (based upon the lower mean body weights of the pups during the lactation period of all three matings). **Study acceptable.** (Moore, 3/21/07)

53004-0006; 223903; "A Preliminary Study of the Effect of M 14360 on Reproduction of the Rat - Dietary Administration"; (P. R. Ryle, R.E. Masters, C.A. Parker; Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Study No. AGR/70; 3/23/90); A preliminary dose range-finding study was performed in which 10 Crl: CD (SD) rats/sex/group received 0, 20, 100, or 500 ppm of M 14360 Technical (batch no. FCF/T/72, purity: 94.6%) in the diet for 4 weeks during a premating period, during mating, and the 3-week gestation and lactation periods. After weaning, the F1 generation offspring received the test material in the diet for an additional 3 weeks. Two dams in the 100 ppm group were euthanized on gestation day 23 and 24 due to dystocia. Another dam in the 500 ppm group suffered total litter loss on day 17 *post-partum*. The mean body weight gain of the 500 ppm parental females during the premating period was reduced ($p<0.01$). The effect persisted through the 3-week gestation period. The mean food consumption of the 500 ppm females were lower than that of the controls during the premating period. The mean litter size of the 500 ppm group was less than that of the controls prior to culling ($p<0.01$). The mean body weight gain of the F1 females was less than that of the controls between 4 and 6 weeks *post-partum*. The mean absolute and relative liver weights of both sexes in the parental generation and the F1 males of the 500 ppm group were greater than those values for the controls ($p<0.01$). The mean relative liver weights for the F1 females in the 500 ppm group was greater than the control value ($p<0.01$). Data were sufficient to establish a

dose range for the guideline two-generation reproduction study. **Study supplemental.** (Moore, 3/15/07)

TERATOLOGY, RAT

** 53004-0005; 223901; "A Study of the Effect of M 14360 on Pregnancy of the Rat"; (P.R. Ryle, D.M. John, I.S. Dawe, A. Anderson; Huntingdon Reseach Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Report No. AGR 47/89915; 11/2/88); Thirty Crl:CD (SD) mated female rats/group were dosed orally by gavage with 0, 5.0, 22.5 or 100 mg/kg/day of M 14360 technical (batch no. FCF/T/72; purity: 94.6%) from day 6 through day 15 of gestation. No deaths resulted from the treatment. The mean body weight gain of the 22.5 and 100 mg/kg dams was less than that of the control group between days 6 and 10 of gestation ($p<0.05$ or 0.01). The mean food consumption was lower for these two groups for the first two days of the treatment and persisted in the 100 mg/kg group through day 9. There was no apparent treatment-related effect on the survival of the fetuses. An increased incidence of unilateral and bilateral hydroureter was noted in the fetuses of the 100 mg/kg group (unilateral, 0: 13.5% vs. 100: 23.5%; bilateral, 0: 9.9% vs. 100: 31.0%; historical control range: unilateral, 8.1 to 23.9%, bilateral, 2.8 to 16.2%). In addition, there was an increased incidence of the 14^{th} rib(s) in the fetuses of the 100 mg/kg group (13/14, 0: 0% vs 100: 13.8%, 14/14, 0: 0% vs. 13.8%). Eighteen of the 24 litters in the 100 mg/kg group had fetuses with this abnormality. **No adverse effect indicated. Maternal NOEL:** 5.0 mg/kg/day (based upon the lower body weight gain and reduced food consumption of the 22.5 mg/kg dams); **Developmental NOEL:** 22.5 mg/kg/day (based upon the increased incidence of fetal abnormalities in the 100 mg/kg group); **Study acceptable.** (Moore, 6/5/07)

TERATOLOGY, RABBIT

** 53004-0005; 223902; "A Study of the Effect of M 14360 on Pregnancy of the Rabbit"; (P.R. Ryle, D.M. John, A. Anderson, I.S. Dawe; Huntingdon Reseach Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Report No. AGR78/9049; 4/9/90); Sixteen New Zealand White rabbits were dosed orally by gavage with 0, 7.5, 15 or 30 mg/kg/day of M 14360 technical (batch no. FCF/T/72; purity: 94.6%) from day 6 through day 18 of gestation. No deaths resulted from the treatment. There was no treatment-related effect upon body weight gain or food consumption over the course of the study. The development of the fetuses was not affected by the treatment. **No adverse effect indicated. Maternal NOEL:** 30mg/kg/day (based upon the lack of treatment-related effects noted in the 30 mg/kg group); **Developmental NOEL:** 30 mg/kg/day (based upon the lack of treatment-related effects on the fetuses in the 30 mg/kg group); **Study acceptable.** (Moore, 6/6/07)

GENE MUTATION

** 53004-0010; 223911; "M 14360 Technical Batch No. 19880/64: Testing for Mutagenic Activity with *Salmonella typhimurium* TA 1535, TA 1537, TA 98, and TA 100 and *Escherichia coli* WP2*uvr*A"; (C.G. Riach; Inveresk Research International, Tanent, EH33 2NE, Scotland; Report No. 10485; 8/19/94); *S. typhimurium* TA98, TA100, TA1535, and TA1537 and *E. coli* WP2*uvr*A strains were preincubated for 20 minutes, followed by treatment for 48 hours at 37° C with M 14360 Technical (batch No. 19880/64; purity: 95.1%) at concentrations ranging from 25 to 800 ug/plate in the 1^{st} trial and from 18.8 to 600 ug/plate in the 2^{nd} trial under conditions of non-activation and activation. Two trials were performed with 3 plates/treatment level. An S9 fraction derived from the liver of rats pretreated with Aroclor 1254 was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. **No adverse effect indicated.** The positive controls were functional. **Study acceptable**. (Moore, 3/30/07)

** 53004-0010; 223913; "An Assessment of the Mutagenic Potential of Using the Mouse Lymphoma TK Locus Assay"; (J.A. Allen, *et. al.*; Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Study No. AGR 54/8923; 6/22/89); Mouse lymphoma L5178Y cells (clone 3.7.2 ($TK^{+/-}$)) were treated with M 14360 technical (batch no. FCF/T/72; purity: 94.6%) at concentrations ranging from 1 to 125 ug/ml in the 1^{st} trial and at concentrations ranging from 10 to 85 ug/ml under conditions of non-activation and activation for 3 hours at 37° C. Two independent trials were performed with duplicate cultures/treatment level and 3 replicates per

culture. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. Cell viability, survival and mutation frequency for each treatment level were determined and compared to those of the solvent control. The results for the two trials did not indicate a treatment-related increase in mutation frequency. **No adverse effect indicated.** The positive controls were functional. **Study acceptable.** (Moore, 4/3/07)

CHROMOSOME EFFECTS

** 53004-0010; 229912; "Analysis of Metaphase Chromosomes Obtained from CHO Cells Cultured *In Vitro* and Treated with M 14360"; (P.C. Brooker, *et. al.*; Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Study No. AGR 52/89244; 6/29/89); Chinese Hamster Ovary cells (K_1-BH_4) were incubated with M 14360 technical (batch no. FCF/T/72; purity: 94.0%) at concentrations ranging from 0.5 to 250 ug/ml under conditions of non-activation and activation at 37° C. The nonactivated samples received 6, 24 or 48 hours of treatment. Those samples treated for 6 hours were incubated for an additional 18 hours. The activated samples received 6 hours of treatment followed by 18 hours of additional incubation. In both assays, the cells were incubated the last 3 hours with Colcemid prior to fixation. The 48 hour treatment under conditions of non-activation was repeated at concentrations of the test material ranging from 5 to 60 ug/ml. All of the incubations were performed with duplicate cultures except for the vehicle controls which were incubated in quadriplicate. 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. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 4/2/07)

DNA DAMAGE

** 53004-0010; 223914; "Mouse Micronucleus Test on M 14360"; (R.J. Proudlock, P. Haynes, K. Meaking; Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Study No. AGR 53/881637; 6/14/89); Fifteen CD-1 mice/sex/group were dosed orally by gavage with 0 (aqueous 1% methyl cellulose), 185, 370 or 740 mg/kg of M 14360 technical (batch no. FCF/T/72; purity: 94.6%). Five animals/sex/group/time point were euthanized at 24, 48 and 72 hours post-dose. In addition, 5 animals/sex/group were dosed with 12 mg/kg of mitomycin C (positive control) and euthanized at 24 hours post-dose. Bone marrow samples from the femurs of each animal were examined and 1000 polychromatic erythrocytes (PCE) per animal were examined for micronuclei. The ratio of PCE's to mature erythrocytes 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, 4/4/07)

** 53004-0010; 223915; "Assessment of Unscheduled DNA Repair Synthesis in Mammalian Cells after Exposure to M 14360"; (R.J. Proudlock; Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Study No. AGR 55/881800; 7/10/88); Hela S3 cells were exposed to M 14360 technical (batch no. FCF/T/72; purity: 94.6%) at concentrations ranging of 0.25 to 512 ug/ml for 3 hours at 37° C under conditions of non-activation and activation. Two trials were performed with duplicate plates for each treatment level. An S9 fraction derived from the liver of rats pretreated with Aroclor 1254 was used to metabolize the test material. There was no apparent treatment-related increase in the net grain count under conditions of either non-activation or activation. **No adverse effect indicated.** The positive controls were functional. **Study acceptable.** (Moore, 4/4/07)

NEUROTOXICITY

No studies submitted.

SUBCHRONIC TOXICITY STUDIES

Rat 4-Week Oral Toxicity Study

53004-0004; 223896; "M14360: Toxicity to Rats by Repeated Oral Administration for 4 Weeks"; (G.A. Dean, *et. al.*; Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Report No. AGR 24/871709; 10/26/88); Five Crl:CD rats/sex/group were dosed orally by gavage with 0, 70, 200 or 500 mg/kg/day of M 14360 Technical (batch no. FCF/T/59, purity: 92%) for 4 weeks. All of the animals in the 500 mg/kg group and 3 females in the 200 mg/kg group were euthanized for moribundity within 3 days of the study initiation. A fourth female was euthanized during the 3rd week due to moribundity as well. The mean body weight of the males in the 200 mg/kg group was less than that of the controls through out the treatment period. The hematology data did not indicate an apparent treatment-related effect. In the clinical chemistry evaluation, the mean serum glucose levels were lower for both sexes in the 70 mg/kg group and for the males in the 200 mg/kg group ($p<0.01$ or 0.001). The total protein and albumin levels of the males in the 70 and 200 mg/kg group were greater than that of the control ($p<0.05$ or 0.01). The globulin levels for the 70 mg/kg females and the 200 mg/kg males were increased as well ($p<0.01$). In the necropsy examination, the mean liver weights were increased for both sexes in the 70 mg/kg group and for the males in the 200 mg/kg group (the one survivor among the females in the 200 mg/kg group also had an increased liver weight) ($p<0.01$). Target tissue: liver; The presence or absence of adverse effects was not determinable due to the lack of histopathology, particularly on the liver. **4-Week Rat Oral Toxicity NOEL:** < 70 mg/kg/day (based upon the effects on the liver and the serum glucose levels of both sexes in the 70 mg/kg/day group); **Study supplemental** (non-guideline study). (Moore, 1/24/07)

Rat 4-Week Dietary Toxicity Study

53004-0004; 223897; "M14360: Preliminary Toxicity to Rats by Dietary Administration for 4 Weeks"; (R. Mayfield, *et. al.*; Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Report No. AGR 21/871271; 12/15/88); Ten Crl:CD rats/sex/group received 0, 40, 160, 640, 2500 or 10000 ppm of M 14360 Technical (batch no. FCF/T/59, purity: 92%) in the diet for 4 weeks ((M) 0, 4.4, 17.5, 68.4, 229 mg/kg/day, (F) 0, 3.8, 16.0, 62.3, 217 mg/kg/day). All of the animals in the 10000 ppm group were euthanized in moribund condition within 5 days of the study initiation. The mean body weight gains for both sexes in the 2500 ppm group and the females in the 640 ppm group through out the study were less than those of the controls ($p<0.01$). The food consumption for these animals was less than that of the controls over this period. The hematology data did not indicate an apparent treatment-related effect. In the clinical chemistry evaluation, the serum glucose levels for both sexes in the 2500 ppm group and the males in the 640 ppm group were less than that of the controls ($p<0.05$ or 0.01). The total protein and globulin levels in the serum of the males in the 640 and 2500 ppm groups were greater than those of the controls ($p<0.05$ or 0.01). The mean absolute and relative liver weights of the 40 ppm males and above and the 640 and 2500 females were greater than that of controls ($p<0.05$ or 0.01). The mean relative kidney weights of the 40 ppm males and above and the 160 ppm females and above were greater than that of the controls ($p<0.05$ or 0.01). In the histopathological examination, a dose-related enlargement of centrilobular to midzonal hepatocytes in the liver of both sexes of the 160 ppm group and above was noted ((M) 0: 0/10 vs. 160: 3/10, 640: 8/10, 2500: 10/10, (F) 0: 0/10 vs. 160: 5/10, 640: 10/10, 2500: 10/10). The livers of both sexes in the 2500 ppm group exhibited fine vacuolation of centrilobular to midzonal hepatocytes ((M) 0: 0/10 vs. 2500: 8/10, (F) 0: 0/10 vs. 2500: 6/10). Target organ: liver. **No adverse effect indicated. 4-Week Rat Dietary NOEL:** (M/F) 40 ppm ((M) 4.4 mg/kg/day, (F) 3.8 mg/kg/day) (based upon the enlargement of hepatocytes in the livers of both sexes in the 160 ppm group); **Study supplemental** (non-guideline study). (Moore, 1/25/07)

53004-0004; 223898; "M14360: Toxicity to Male Rats by Dietary Administration for 4 Weeks"; (S.J. Crome, *et. al.*; Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Report No. AGR 25/88970; 10/18/89); Ten Crl:CD male rats/group received 0, 2, 5, 15 or 40 ppm of M 14360 Technical (batch no. FCF/T/59, purity: 90.9% (8/10/87), 90.4% (1/26/88)) in the diet for 4 weeks (0, 0.21, 0.52, 1,57, 4.19 mg/kg/day). No deaths resulted from the treatment. The mean body weights and food consumption were not affected by the treatment through out the study. Although the serum GOT and GDH activities of the 40 ppm group were elevated above those of the control, these effects were not toxicologically significant. There were

no treatment-related effects upon liver weights or the incidence of lesions in the liver. **No adverse effect indicated. 4-Week Rat Dietary NOEL:** (M) 40 ppm (4.2 mg/kg/day) (based upon the lack of treatment-related effects at the highest dose tested); **Study supplemental** (non-guideline study). (Moore, 1/2507)

Rat Subchronic Dietary Toxicity Study

53004-0005; 223899; "M14360: Toxicity to Rats by Dietary Administration for 13 Weeks"; (R. Mayfield, *et.al*; Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Report No. AGR 23/881322; 12/19/88); Ten Crl:CD rats/sex/group received 0, 10, 60 or 360 ppm of M 14360 Technical (batch no. FCF/T/65, purity: 93.1%) for 13 weeks ((M) 0, 0.7, 4.1, 23.9 mg/kg/day, (F) 0, 0.9, 5.5, 28.7 mg/kg/day). There were no deaths during the study. The mean body weight gain of the 360 ppm females was less than that of the controls over the course of the study ($p<0.05$). There was no treatment-related effect on the mean food consumption. The ophthalmology examination did not reveal any treatment-related lesions. The hematology and urinalysis evaluations did not indicate any treatment-related effects on the blood. In the clinical chemistry evaluation, the serum cholesterol levels for both sexes in the 360 ppm group were greater than those of the controls ($p<0.05$ or 0.01). The mean relative liver weights of both sexes in the 360 ppm group and the females in the 60 ppm group were greater than the control values ($p<0.05$ or 0.01). In the histopathological examination, enlargement of the centrilobular hepatocytes was noted in the livers of both sexes in the 360 ppm group and the 60 ppm males ((M) 0: 0/10 vs. 60: 5/10, 360: 10/10, (F) 0: 0/10 vs. 360: 10/10, $p<0.05$ or 0.01). Target organ: liver. **No adverse effect indicated. Rat Subchronic Dietary Toxicity NOEL:** (M/F) 10 ppm ((M) 0.7 mg/kg/day, (F) 0.9 mg/kg/day) (based upon the incidence of centrilobular hepatocyte enlargement in the 60 ppm treatment group); **Study acceptable.** (Moore, 1/26/07)

Mouse Subchronic Dietary Toxicity Study

53004-0004; 223895; "M14360: Toxicity to Mice by Dietary Administration for 13 Weeks"; (R. Mayfield, *et. al.*; Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Report No. AGR 49/89715; 9/15/89); Ten CD-1 mice/sex/group received 0, 5, 25, 125 or 625 ppm of M 14360 Technical (batch no. FCF/T/72; purity: 94.6%) in the diet for 13 weeks ((M) 0, 1, 4, 16, 85 mg/kg/day, (F) 1, 4, 20, 103 mg/kg/day). No deaths resulted from the treatment. The mean body weights, food consumption or water consumption were not apparently affected by the treatment. In the clinical chemistry evaluation, the mean SGPT activity was increased for both sexes in the 625 ppm group and for the females in the 125 ppm group ($p<0.05$ or 0.01). The mean SGOT activity was increased for the females in the 125 and 625 ppm groups ($p<0.01$). The mean liver weights were increased for both sexes in the 625 ppm group and for the females in the 125 ppm group ($p<0.01$). There was an increased incidence and severity of centrilobular hepatocyte enlargement in both sexes of the 25 ppm group and above ((M) 0:0/10 vs. 25: 7/10, 125: 9/10, 625: 10/10; (F) 0: 0/10 vs. 25: 6/10, 125: 10/10, 625: 10/10). The females in the 625 ppm group also exhibited midzonal hepatocyte vacuolation (0: 0/10 vs. 625: 3/10). Single cell necrosis in the liver was noted for the females in the 125 ppm group and for both sexes in the 625 ppm group ((M) 0: 0/10 vs. 625: 2/10, (F) 0: 0/10 vs. 125: 4/10, 625: 2/10). Single cell degeneration was noted in the livers of both sexes in the 125 ppm and the 625 ppm groups ((M) 0: 0/10 vs. 125: 2/10, 625: 5/10, (F) 0: 0/10 vs. 125: 1/10, 625: 2/10). Necrosis was observed in the livers of the 125 ppm females and both sexes in the 625 ppm group ((M) 0: 0/10 vs. 625: 2/10, (F) 0: 0/10 vs. 125: 1/10, 625: 2/10). The kidneys of the 625 ppm males exhibited a peripelvic aggregation of lymphocytes (0: 0/10 vs. 625: 3/10). **Possible adverse effect:** liver necrosis. **Subchronic dietary NOEL:** (M/F) 5 ppm ((M/F) 1 mg/kg/day) (based upon the incidence of centrilobular hepatocyte enlargement in the liver of both sexes in the 25 ppm treatment group); **Study supplemental** (study did not include all of the parameters required in a guideline subchronic dietary study). (Moore, 1/22/07)

Rabbit 21-Day Repeated Dosing Dermal Toxicity Study

53004-0005; 223900; "A 21-Day Repeated Dose Dermal Toxicity Study in Albino Rabbits with M 14360 125 SL"; (M.D. Gelin, J. Laveglia; Ricera, Inc., Department of Toxicology and Animal Metabolism, Painesville, OH; Doc. No. 3842-91-0064-TX-002; 6/16/92); The skin of six New

Zealand White rabbits/sex/group was exposed to 0, 250, 1000 or 2000 mg/kg/day of M 14360 125 SL (batch no. FCF/T/99-91, a.i.: 125 g/l) for 6 hours/day for 21 days under a semi-occlusive wrap. No treatment-related deaths occurred during the study. There were no treatment-related effects upon the mean body weights or food consumption. Signs of erythema progressed to grade 2 (well-defined) in a dose-related manner at the site of application for all of the treatment groups. Very slight edema was reported for one 1000 mg/kg male and very slight to well-defined edema was noted for three 2000 mg/kg males and one 2000 mg/kg female. The hematology and clinical chemistry evaluations did not reveal any treatment-related effect. In the necropsy, no effect was noted on the absolute or relative organ weights. In the histopathology examination, acanthosis was noted at the site of application for 3 of the males and 4 of the females in the 2000 mg/kg group. **No adverse effect indicated. Rabbit 21-Day Repeated Dosing Dermal Toxicity:** (M/F) 2000 mg/kg/day (based upon the lack of a treatment-related effect in the 2000 mg/kg treatment group); **Dermal Irritation NOEL for Repeated Dosing:** (M/F) <250 mg/kg (based upon the incidence of erythema at the site of application in the 250 mg/kg group); **Study acceptable.** (Moore, 6/1/07)

Dog 4-Week Dietary Toxicity Study

53004-0007; 223905; " M 14360 Dose-Range Finding Preliminary Toxicity Palatability Study in Beagle Dogs (Final report - repeated daily dosage for 4 weeks)"; (P. Burford, T. McLean, D.P. Buist, D. Crook; Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Report No. AGR 51/89813; 1/22/91); One beagle dog/sex/group received 270, 360 or 720 ppm of M 14360 Technical (batch no. FCF/T/72; purity: 94.6%) in the diet for 4 weeks. No animals died during the treatment. Food consumption by the two animals in the 720 ppm group was lower at various times during the four week study. The two animals lost weight during the treatment period. The body weight gain and food consumption of the animals in the two lower treatment groups were not apparently affected by the treatment. Serum alkaline phosphatase activity levels were elevated for the animals in the 270 ppm group (only group for which data were available). Treatment levels of 22.5, 90 and 360 ppm were selected for the guideline dog chronic toxicity study based on these data. **Study supplemental.** (Moore, 3/21/07)

RAT METABOLISM

Metabolism, Rat

53004-0011; 223917;"Study of the Excretion and Distribution of Radiolabel following Oral Administration of Phenyl-^{14}C-ASC-66811 to Sprague-Dawley Rats"; (M.C. Savides, J.P. Marciniszyn, J.C. Killeen; Ricera, Inc., Department of Toxicology and Animal Metabolism, Painesville, OH; Doc. No. 2050-89-0303-AM-001; 6/22/90); Two Crl:CD rats/sex/group were dosed orally by gavage with 5 or 60 mg/kg of [U-^{14}C-phenyl]-ASC-66811 (M14360) (no batch no. reported, radiochemical purity: 99.3% (TLC), 99.0% (HPLC)). Unlabelled ASC-66811 (batch no. FCF/T/72, purity: 94.0%) was used to adjust the specific activity of the dosing preparations. Urine, carbon dioxide, and fecal samples were collected at designated intervals up to 168 hours post-dose. The distribution of radiolabel in the tissues was examined at 168 hours post-dose. Excretion via the urine was the primary pathway with 70 to 79% of the administered radiolabel recovered in the urine. Twenty one to 32% of the radiolabel was recovered in the feces. At the lower dosing level, 70 and 57% of the administered dose was excreted within the 1st 24 hours post-dose for the males and females, respectively. At the higher dose, 64 and 21% of the dose was excreted during the 1st 24 hours for the males and female, respectively. Recovery of the radiolabel in the exhaled air was minimal. The residual radiolabel in the tissues constituted less than 1% of the dose. The kidneys were the primary site of recovery at 7 days post-dose. **Study supplemental.** (Moore, 4/6/07)

53004-0011; 223918; "Study to Identify the Metabolites of [^{14}C]-Phenyl Labeled M 14360 in Rats"; (D.Y. Lee, B. McCall; Ricera, Inc., Department of Environmental and Metabolic Fate, Painesville, OH; Doc. No. 5085-91-0341-AM-001; 3/30/95); Pooled urine and fecal samples derived from the first 48 hours post-dose of both single dose and multiple dose treatment regimens in which Crl:CD BR rats of both sexes were dosed orally by gavage with 5 or 60 mg/kg of [^{14}C]-Phenyl M 14360 (lot no. 140, radiochemical purity: 97.99%, specific activity: 37.33

mCi/mmole) (see doc. no. 5083-91-0339-AM-001-001, vol. no. 53004-0013, rec. no. 223927 and doc. no. 5084-91-0340-AM-001-001, vol. no. 53004-0013, rec. no. 223928) were analyzed for radiolabeled metabolites by means of GC/MS. Oxidation and reduction of the parent compound resulted in the recovery of the M 14360 acid in the urine and the M14360 alcohol in the feces of both sexes at both treatment levels for both treatment regimens. Displacement of the triazole ring from the parent compound by glutathione and subsequent metabolism resulted in the recovery of the sulfoxide (P1) and the N-acetylcysteine (P4) conjugates. P1, P4 and M 14360 acid were recovered in the urine. P4, M 14360 and M 14360 alcohol were recovered in the feces. Additional metabolites, P2 and P3, were recovered in the urine and P5 was isolated in the feces. The structures of these moieties were not elucidated. The unidentified radiolabeled moieties constituted 15 to 33% of the administered dose for both treatment levels under both treatment regimens. **Study supplemental.** (Moore, 4/12/07)

53004-0011; 223919; "Study of the Excretion and Distribution of Radiolabel following Oral Administration of Triazole-^{14}C-ASC-66811 to Sprague-Dawley Rats"; (M.C. Savides, J.P. Marciniszyn, J.C. Killeen, Jr.; Ricera, Inc., Department of Toxicology and Animal Metabolism, Painesville, OH; Doc. No. 2045-89-0180-AM-001; 6/22/90); Two Crl:CD rats/sex/group were dosed orally by gavage with 5 or 60 mg/kg of Triazole-^{14}C-ASC-66811 (M14360) (no batch no. reported, radiochemical purity: >99%, specific activity: 42 mCi/mmole). Unlabelled ASC-66811 (batch no. 15099/28, purity: 99.7%) was used to adjust the specific activity of the dosing preparations. Urine, carbon dioxide, and fecal samples were collected at designated intervals up to 168 hours post-dose. The distribution of radiolabel in the tissues was examined at 168 hours post-dose. Excretion via the urine was the primary pathway with 79 to 95% of the administered radiolabel recovered in the urine. Twelve to 16% of the radiolabel was recovered in the feces. At the lower dosing level, 61 and 27% of the administered dose was excreted within the 1st 24 hours post-dose for the males and females, respectively. At the higher dose, 28 and 8% of the dose was excreted during the 1st 24 hours for the males and female, respectively. Recovery of the radiolabel in the exhaled air ranged from 0.13 to 0.23% of the administered dose for both dose levels. The residual radiolabel in the tissues ranged from 0.7 to 1.9% of the administered dose. The radiolabel was not sequestered in a particular tissue at 7 days post-dose. **Study supplemental.** (Moore, 4/13/07)

53004-0011; 223920; "Study to Identify the Metabolites of [^{14}C]-Triazole Labeled M 14360 in Rats"; (D.Y. Lee, B. McCall; Ricera, Inc., Department of Environmental and Metabolic Fate, Painesville, OH; Doc. no. 3786-0093-AM-001; 3/30/95); Pooled urine and fecal samples derived from the first 48 hours post-dose of both single dose and multiple dose treatment regimens in which Crl:CD BR rats of both sexes were dosed orally by gavage with 5 or 60 mg/kg of [^{14}C]-Triazole M 14360 (see doc. no. 3771-90-0489-AM-001, vol. no. 53004-0012, rec. no. 223925 and doc. no. 3772-90-0490-AM-001-001, vol. no. 53004-0012, rec. no. 223926) were analyzed for radiolabeled metabolites by means of GC/MS. The major metabolite in both the urine and the feces was the triazole. In the urine of males treated with either the single dose or multiple dose regimen, triazole constituted 92 to 95% of radiolabel which was recovered. For the females, the percentages ranged from 72 to 83% of the recovered radiolabel. Other metabolites which were recovered in the urine of the females were the M 14360 acid (12 to 20%), M3 (the glucuronide adduct of the acid) (3 to 6%) and to a lesser extent the M 14360 alcohol (1 to 4%). The M 14360 acid was also identified in the urine of the males (5 to 7%). Triazole constituted 64 and 69% of the radiolabel recovered in the feces of the males and females receiving the single low dose regimen, respectively. The percentages increased to 86 and 81% for the males and females dosed with 60 mg/kg. In the multiple dose regimen, the percentage of the radiolabel recovered as triazole declined to 27 and 28% for the males and the females on the lower dose regimen and to 60 and 65% for the higher dose regimen, respectively. Among the other metabolites recovered in the feces, the M 14360 acid, the M 14360 alcohol and the parent compound were identified. These results indicate the cleavage of either the difluoroethane or the triazole moiety from the parent compound as a primary step in its metabolism. **Study supplemental.** (Moore, 4/18/07)

53004-0011; 223921; "Pilot Toxicokinetic Study with [^{14}C]-Phenyl M 14360"; (J.C. Andre, J.P. Marciniszyn, J. Laveglia; Ricera, Inc., Department of Toxicology and Animal Metabolism,

Painesville, OH; Doc. No. 5081-91-0337-AM-001; 1/27/93); Three Crl:CD BR rats/sex/group were dosed orally by gavage with 5 or 60 mg/kg of [^{14}C]-Phenyl M 14360 (lot no. 140, radiochemical purity: 96.90%, specific activity: 37.35 mCi/mmole). Unlabeled M 14360 technical (lot no. 18873/37, purity: 97.6%) was used to adjust the specific activity of the dosing preparations. One animal/sex was dosed with the vehicle alone. Blood was drawn at specified times post-dose from each of the study animals. The radiolabel recovered from each sample was determined by combustion of the sample and recovery of the radiolabeled carbon dioxide which was then analyzed by liquid scintillation counting. The maximal blood concentration of the radiolabel could not be determined because the highest level of radioactivity was recorded for the first sample time in each of the treatment groups. The reported half-lives for the radiolabel in the blood were comparable for all of the treatment groups with a mean for all of the groups of 16.3 hours. Likewise the rates of elimination were comparable with the mean value being 0.044 ng equivalents/g/hour. **Study supplemental.** (Moore, 4/18/07)

53004-0011; 223922; "Toxicokinetic Study with [^{14}C]-Phenyl M 14360"; (J.C. Andre, D.B. Johnson, J. Laveglia; Ricera, Inc., Department of Toxicology and Animal Metabolism, Painesville, OH; Doc. No. 5082-91-0338-AM-001; 3/12/93); Five Crl:CD BR rats/sex/group were dosed orally by gavage with 5 or 60 mg/kg of [^{14}C]-Phenyl M 14360 (lot no. 140, radiochemical purity: 97.99%, specific activity: 37.33 mCi/mmole). Unlabeled M 14360 (lot no. 18873/37, purity: 97.6%) was used to adjust the specific activity of the dosing preparations. Two animals/sex were dosed only with the vehicle. Urine, feces and cage wash samples were collected from each of the groups at designated time intervals after treatment. The animals were euthanized at 72 hours post-dose. The time-to-peak blood levels for the radiolabel ranged from 1.2 hours post-dose for the 5 mg/kg males to 19.2 hours post-dose for the 60 mg/kg females. The half-life in the blood was approximately 15 hours for all of the treatment groups. The urine was the primary pathway of excretion with 62 to 70% of the administered dose being recovered in the urine and cage wash by 72 hours post-dose for both treatment levels. The recovery in the feces from these groups ranged from 25 to 36%. At 72 hours post-dose, 2.8 to 5.8% of the administered dose was recovered in the tissues. The gastrointestinal tract and the liver were the primary sites of recovery. **Study supplemental.** (Moore, 4/19/07)

53004-0012; 223923; "Pilot Toxicokinetic Study with [^{14}C]-Triazole M 14360"; (J.C. Andre, J.P. Marciniszyn, J.C. Killeen; Ricera, Inc., Department of Toxicology and Animal Metabolism, Painesville, OH; Doc. No. 3747-90-0467-AM-001; 4/18/91); Three Crl:CD BR rats/sex/group were dosed orally by gavage with 5 or 60 mg/kg of [^{14}C]-Triazole M 14360 (lot no. 768-35-E, radiochemical purity: 99%, specific activity: 70.7 mCi/mmole). Unlabeled M 14360 technical (batch no. 14644/38, purity: 99.3%) was used to adjust the specific activity of the dosing preparations. Two animal/sex was dosed with the vehicle alone. Blood was drawn at specified times post-dose from each of the study animals. The radiolabel recovered from each sample was determined by combustion of the sample and recovery of the radiolabeled carbon dioxide which was then analyzed by liquid scintillation counting. The time to maximal blood concentrations of radiolabel ranged from 8 hours post-dose for the 5 mg/kg males to between 28 and 36 hours post-dose for the 60 mg/kg females. **Study supplemental.** (Moore, 4/19/07)

53004-0012; 223924; "Toxicokinetic Study with [^{14}C]-Triazole M 14360"; (J.C. Andre, J.P. Marciniszyn, J. Laveglia; Ricera, Inc., Department of Toxicology and Animal Metabolism, Painesville, OH; Doc. No. 3770-91-0015-AM-001; 3/20/92); Five Crl:CD BR rats/sex/group were dosed orally by gavage with 5 or 60 mg/kg of [^{14}C]-Triazole M 14360 (lot no. 768-35-E, radiochemical purity: 99%, specific activity: 70.7 mCi/mmole). Unlabeled M 14360 technical (batch no. 14644/38, purity: 99.3%) was used to adjust the specific activity of the dosing preparations. Two animals/sex were dosed only with the vehicle. Urine, feces and cage wash samples were collected from each of the groups at designated time intervals after treatment. The animals were euthanized at 72 hours post-dose. The median time-to-peak blood levels for the radiolabel ranged from 8 hours post-dose for the 5 mg/kg males to 28 hours post-dose for the 60 mg/kg females. The median half-life in the blood ranged from 9.3 to 11.3 hours for all of the treatment groups. The urine was the primary pathway of excretion with 75 to 83% of the administered dose being recovered in the urine and cage wash by 72 hours post-dose for both

treatment levels. The recovery in the feces from these groups ranged from 12 to 17%. At 72 hours post-dose, 4.1 to 4.9% of the administered dose was recovered in the tissues. The gastrointestinal tract and the liver were the primary sites of recovery. **Study supplemental.** (Moore, 4/20/07)

53004-0012; 223925; "Study of the Elimination and Distribution of Radiolabel following Oral Administration of [^{14}C]-Triazole M 14360 to Sprague-Dawley Rats"; (J.C. Andre, J.P. Marciniszyn, J. Laveglia; Ricera, Inc., Department of Toxicology and Animal Metabolism, Painesville, OH; Doc. No. 3771-90-0489-AM-001; 11/5/92); Ten Crl:CD BR rats/sex/group were dosed orally by gavage with 5 or 60 mg/kg of [^{14}C]-Triazole M 14360 (lot no. 768-35-E, radiochemical purity: 99%, specific activity: 70.7 mCi/mmole). Unlabeled M 14360 (batch no. 14644/38, purity: 99.3%) was used to adjust the specific activity of the dosing preparations. Five animals/sex/group were dosed with the test material and euthanized 7 days after dosing. Five males and 5 females in the 5 mg/kg group were also euthanized at 8 and 18 hours, post-dose, respectively. Five males and 5 females in the 60 mg/kg group were euthanized at 16 and 28 hours post-dose, respectively. Two animals/sex were dosed only with the vehicle. Urine, feces and cage wash samples were collected from each of the groups at designated time intervals after treatment. The urine was the primary pathway of excretion with 80 to 86% of the administered dose being recovered in the urine and cage wash by 7 days post-dose for both treatment levels. The recovery in the feces from these groups ranged from 14 to 18%. At the end of 7 days, 0.9 to 1.5% of the administered dose was recovered in the tissues. For the animals which were euthanized between 8 and 28 hours post-dose, 67 to 85% of the administered dose was recovered in the tissues. At these shorter time intervals, the gastrointestinal tract was the primary site of recovery. Other sites with significant concentrations of the radiolabel were the adrenals, liver, and kidneys. For the females, the ovaries demonstrated a high concentration of the radiolabel as well. By 7 days post-dose, the liver was the primary site of recovery for the males. The radiolabel was well distributed in the tissues of the females at 7 days post-dose. **Study supplemental.** (Moore, 4/16/07)

53004-0012; 223926; "Study of the Elimination and Distribution of Radiolabel following Repeated Oral Administration of [^{14}C]-Triazole M 14360 to Sprague-Dawley Rats; (J.C. Andre, J. Laveglia, amendment: M.C. Savides, M. Watson; Ricera, Inc., Department of Toxicology and Animal Metabolism, Painesville, OH; Doc. no. 3772-90-0490-AM-001-001; 3/21/94, amended, 8/30/00); Ten Crl:CD BR rats/sex/group were dosed orally by gavage with 5 or 60 mg/kg of [^{14}C]-Triazole M 14360 (lot no. 135 A, radiochemical purity: 99.1%, specific activity: 40.7 mCi/mmole). Unlabeled M 14360 (batch no. 18873/37, purity: 97.6%) was used to adjust the specific activity of the dosing preparations. Five animals/sex/group were dosed with the test material and euthanized 7 days after dosing. Five males and 5 females in the 5 mg/kg group were also euthanized at 8 and 18 hours, post-dose, respectively. Five males and 5 females in the 60 mg/kg group were euthanized at 16 and 28 hours post-dose, respectively. Two animals/sex were dosed only with the vehicle. Urine, feces and cage wash samples were collected from each of the groups at designated time intervals after treatment. The urine was the primary pathway of excretion with 85 to 87% of the administered dose being recovered in the urine and cage wash by 7 days post-dose for both treatment levels. The recovery in the feces from these groups ranged from 12 to 16%. At the end of 7 days, 0.6 to 0.9% of the administered dose was recovered in the tissues. For the animals which were euthanized between 8 and 28 hours post-dose, 41 to 86% of the administered dose was recovered in the tissues. At these shorter time intervals, the gastrointestinal tract was the primary site of recovery. The liver was th other site with a significant concentration of the radiolabel. By 7 days post-dose, the liver was the primary site of recovery. **Study supplemental.** (Moore, 4/16/07)

53004-0013; 223927; "Study of the Elimination and Distribution of Radiolabel following Oral Administration of [^{14}C]-Phenyl M 14360 to Sprague-Dawley Rats"; (J.C. Andre, J. Laveglia, amendment: M.C. Savides, M. Watson; Toxicology and Pharmacology, Ricera, LLC, Painesville, OH; Doc. No. 5083-91-0339-AM-001-001; 2/2/95, amended, 2/15/01); Ten Crl:CD BR rats/sex/group were dosed orally by gavage with 5 or 60 mg/kg of [^{14}C]-Phenyl M 14360 (lot no. 140, radiochemical purity: 97.99%, specific activity: 37.33 mCi/mmole). Unlabeled M 14360 (lot no. 18873/37, purity: 97.6%) was used to adjust the specific activity of the dosing preparations.

Five animals/sex/group were dosed with the test material and euthanized 7 days after dosing. Five males and 5 females in the 5 mg/kg group were also euthanized at 1 and 2 hours, post-dose, respectively. Five males and 5 females in the 60 mg/kg group were euthanized at 4 and 18 hours post-dose, respectively. Four animals/sex were dosed only with the vehicle. Urine, feces and cage wash samples were collected from each of the groups at designated time intervals after treatment. The urine was the primary pathway of excretion with 57 to 67% of the administered dose being recovered in the urine and cage wash by 7 days post-dose for both treatment levels. The recovery in the feces from these groups ranged from 33 to 39%. At the end of 7 days, 0.6 to 1.5% of the administered dose was recovered in the tissues. For the animals which were euthanized between 1 and 18 hours post-dose, 69 to 94% of the administered dose was recovered in the tissues. At the shorter time intervals, the gastrointestinal tract was the primary site of recovery. By 18 hours post-dose, the adrenals were the primary site of recovery. The liver and kidneys also had a higher concentration of the radiolabel over the shorter time period. For the females, the ovaries demonstrated a high concentration of the radiolabel as well. By 7 days post-dose, the kidneys were the primary site of recovery, followed by the liver, adrenals and ovaries. **Study supplemental.** (Moore, 4/9/07)

53004-0013; 223928; "Study of the Elimination and Distribution of Radiolabel following Repeated Oral Administration of M 14360 to Sprague-Dawley Rats"; (J.C. Andre, J. Laveglia, amendent, M.C. Savides, M. Watson; Toxicology and Pharmacology, Ricera, LLC, Painesville, OH; Doc. No. 5084-91-0340-AM-001-001; 5/10/95, amended, 2/15/01); Ten Crl:CD BR rats/sex/group were dosed orally by gavage with 5 or 60 mg/kg/day of unlabeled M 14360 (lot no. 18873/37, purity: 97.6%) for 14 days, followed by a single dose of 5 or 60 mg/kg of [^{14}C]-Phenyl M 14360 (lot no. 140, radiochemical purity: 97.99%, specific activity: 37.33 mCi/mmole). The unlabeled M 14360 (lot no. 18873/37, purity: 97.6%) was used to adjust the specific activity of the dosing preparations. Five animals/sex/group were dosed with the test material and euthanized 7 days post-final dose. Five males and 5 females in the 5 mg/kg group were also euthanized at 1 and 2 hours, post-final dose, respectively. Five males and 5 females in the 60 mg/kg group were euthanized at 4 and 18 hours post-final dose, respectively. Two animals/sex were dosed only with the vehicle. Urine, feces and cage wash samples were collected from each of the groups at designated time intervals after treatment. The urine was the primary pathway of excretion with 65 to 75% of the administered dose being recovered in the urine and cage wash by 7 days post-dose for both treatment levels. The recovery in the feces from these groups ranged from 27 to 37%. At the end of 7 days, 0.6 to 1.1% of the administered dose was recovered in the tissues. For the animals which were euthanized between 1 and 4 hours post-dose, 92 to 93% of the administered dose was recovered in the tissues. At 18 hours post-dose, 42% of the radiolabel was retained in the tissues of the females treated with 60 mg/kg. Up through 18 hours post-dose, the gastrointestinal tract was the primary site of recovery in the tissues. The liver, adrenals, and kidneys were also prominent sites of radiolabel recovery. For the females, the ovaries demonstrated a high concentration of the radiolabel as well. By 7 days post-dose, the kidneys were the primary site of recovery, followed by the liver, adrenals and ovaries. **Study supplemental.** (Moore, 4/10/07)

53004-0014; 223929; "(1) ^{14}C-Tetraconazole: Excretion Study in the Rat after Single Oral Administration, (2) Further Investigation in Excreta of Rats after ^{14}C-Tetraconazole Administration, to Ascertain the Presence of S-5 and S-6 Metabolites, (3) Experimental Addendum to ABT.98.08 Study"; ((1) A. Triolo, (2, 3) F.C. Castoldi, G. Pizzingrilli; (1) Istituto di Recerche Biomediche, "A. Marxer" RBM S.p.A., 10010 Colleretto Giacosa (TO), Italy; (2, 3) ISAGRO RICERCA Srl, Biochemistry & Toxicology, Biochemistry Unit, 28100 Novara, Italy; (1) Exp. No. 980472, (2) Doc. No. R/ABT.98.08; (1) 6/26/98, (2) 7/8/98, (3) 5/28/99); Three Sprague-Dawley rats/sex were dosed orally by gavage with 1.25 mg/kg of [^{14}C-U-triazolyl] tetraconazole (lot no. 161/a, radiochemical purity: 96.34%, specific activity: 41.72 uCi/mg). Unlabeled tetraconazole was used to adjust the specific acitivity of the dosing preparation to 50 uCi/kg. Urine and feces were collected at specific time intervals up to 72 hours post-dose. Urine was the primary route of excretion with 71 and 62% of the administered dose recovered there for the males and females, respectively. An additional 19 and 26% was recovered in the feces of the males and females respectively. The primary metabolite recovered in the urine was triazole (64 and 41% for the

males and females, respectively). β-glucuronidase-mediated hydrolysis of the urine samples did not greatly alter the metabolic profile. Unmetabolized tetraconazole was the primary radiolabeled moiety recovered in the feces of the females, 8.8% of the administered dose. M14360-DCP-3OH was the primary metabolite in the feces of the males, 3.5% of the administered dose, followed by triazole (1.9%) and M14360-DCP-5OH (1.2%). In the Experimental Addendum to ABT.98.08, M14360-DFA was identified in the urine of the female rats. This recovery constituted 1.2% of the administered dose. **Study supplemental.** (Moore, 4/27/07)