CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Tolfenpyrad

Chemical Code # 6055, **Tolerance #** 53141
SB 950 # NA

Original: 11/18/11
Revised: 1/26/12

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, no adverse effect indicated
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, possible adverse effect
DNA damage:	No data gap, no adverse effect indicated
Neurotoxicity:	No data gap, no adverse effect indicated

Toxicology one-liners are attached.

All record numbers through #257089 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T120126
Revised by T. Moore

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

COMBINED, RAT

53141-0123, 257049;" A Chronic Toxicity/Carcinogenicity Study of OMI-88 Technical in Rats by Dietary Administration" Chida,T., et. Al., 9/28/99, Kashima Laboratory, Kashima-gun, Ibaraki, Japan, Project ID: T-10013, 6L792. OMI-88 Technical (Lot No. 6D-01-2), 99.33% white powder. Sixty Fisher rats (F344/DuCrj, SPF) /sex/group were exposed to test diets containing OMI-88 Technical at dosages of 0, 15, 40, or 80 ppm for up to 24 months [mean test material consumption of the 15, 40 or 80 ppm group was 0.561, 1.50 or 3.07 mg/kg/day for males and 0.686, 1.85 or 3.79 mg/kg/day for females, respectively]. An interim necropsy was done on 10 rats/group at week 53 of administration. There were no test substance treatment related mortalities, clinical signs, or changes in clinical pathology, urinalysis and ophthalmology examinations. Decreased body weight and food consumption were observed in the high dose males and the 40 and 80 ppm group females. Increased relative weights of liver and kidney were observed in the high dose males and females at week 53 and 105. In the 40 ppm group males, increased relative weight of liver was also observed at week 105, increased relative weight of kidneys was seen at weeks 53 and 105. Necropsy findings indicated color changes of kidney and Harderian gland in the high dose animals. White patches of liver were seen in the 40 ppm group females. Brownish Harderian gland was seen also in the 40 ppm group males and females. There were no test substance treatment related neoplasm findings. Increased hyaline droplets in proximal tubular epithelium of kidney were observed in 40 and 80 ppm group males at week 53. Histological findings (non-neoplasms) at week 105 included increased incidence of sinus histiocytosis of mesenteric lymph node, kidney proximal tubule epithelium hypertrophy and Harderian gland hypersecretion in the high dose males and females. Increased incidence of sinus histiocytosis of mesenteric lymph node was also seen in the female 40 ppm group animals. Increased mast cell in mesenteric lymph node was seen in the high dose males at week 105. Special stains described in IV. A. 18 did not identify any unusual pathology. **NOEL: 15 ppm (0.561 mg/kg/day for males and 0.686 mg/kg/day for females) for Fisher rats (F344/DuCrj, SPF) in the 24-month chronic toxicity/carcinogenicity study with OMI-88 Technical (based on renal histological findings: males - hyaline droplets; females – proximal tubular epithelium hypertrophy). No adverse effect. **Acceptable** (Pan, 5/10/11).

CHRONIC TOXICITY, RAT

See Combined, Rat above.

CHRONIC TOXICITY, DOG

**53141-0121, 257047;" A 52-Week Oral Chronic Toxicity Study of OMI-88 Technical in Beagle Dogs" Nagashima, Y., 9/14/99, Bozo Research Center, Shizuoka-ken, Japan, Project ID: T-10020, B-3949. OMI-88 Technical (Lot No. 6D-01-2), 99.33% white powder. Four Beagle dogs/sex/group were exposed to OMI-88 Technical orally at dosages of 0, 1, 5, or (initially) 20 mg/kg/day once daily for 52 weeks. The high dose group was given 20 mg/kg/day for the first 4 weeks and then 10 mg/kg/day thereafter. In the high dose group 1 male and 1 female died at week 12 and 4, respectively. Increased incidences of abnormalities of stool (soft, watery, and mucous stool) and salivation were observed in the 5 and 20/10 mg/kg/day group dogs. These clinical signs were the basis of the NOEL of 1 mg/kg/day in both sexes. In the dogs that died during the study, clinical signs including "no defecation", emaciation, and decreased spontaneous movement were observed before their deaths. Absent or severely reduced food consumption and other signs of moribund condition preceded death. "No defecation" and emaciation were also noted in another high dose surviving female dog. Decreased body weight was observed in high dose males from week 4 to 11, corresponding to decreased food consumption from week 4 to 12 in the males of this group. In the high dose group female dogs, the body weight decrease was observed between weeks of 3 to 13,

and from week 26 to 52. Decreased food consumption in the high dose females occurred from week 3 to 9, and intermittently reduced food consumption was observed in this group of females from week 26 to 52. There was less fluctuation in the food consumption in the high dose males from week 25 to 52. Histopathological examinations revealed increased cytoplasmic eosinophilia of hepatocytes in the livers of the high dose males and females. Increased vacuolation in tubular epithelium of kidney and increased eosinophilic hypertrophy of tubular epithelium in the kidney was observed in the high dose male decedent. **NOEL**: 1 mg/kg/day due to the increased incidence of salivation and abnormal stools. **Acceptable** (Pan, 4/29/11).

ONCOGENICITY, RAT

See Combined, Rat above.

ONCOGENICITY, MOUSE

53141-0122, 257048;" 78-Week Dietary Oncogenicity Study in Mice with OMI-88 Technical" Ivett, J., 10/5/99, Covance Laboratories Inc., Vienna, Virginia 22182-1699, Laboratory Study ID: Covance 6287-110, T-10016. OMI-88 Technical (Lot No. 6D-01-2), 99.33% white powder. Fifty Crl:CD-1® (ICR)BR albino mice/sex/group were exposed to test diets containing OMI-88 Technical at dosages of 0, 15, 150, or 500/400/300 ppm once daily for 78 weeks [mean test material consumption was 2.2, 20.8, and 60.9 mg/kg/day for males and 2.8, 27.1, and 75.9 mg/kg/day for females 15, 150 and 500/400/300 ppm groups, respectively]. The high dose, 500/400/300 ppm group, was given 500 ppm for the first 12 weeks and then 400 ppm from week 13 to 19, then 300 ppm from week 20 to 79. Hunched posture and thin appearance were observed in the 500 ppm animals during the first 12 weeks of the study. Hypoactivity, few feces and paleness were noted in the 500 ppm females. Thus the high dose level was reduced to 400 ppm at week 13. Treatment related clinical signs including hunched appearance, thin appearance and hypoactivity were observed in the 400 ppm group animals during the following 7 weeks. Therefore, the high dose animals received 300 ppm OMI-88 technical from week 20 for the remainder of the study. Decreased body weight was observed in the high dose mice and the 150 ppm group males throughout the study. Food consumption was decreased in the high and mid-dose group mice throughout the study. No test substance related changes in hematology, necropsy and pathology examinations. **NOEL**: 15 ppm (2.2 mg/kg/day for males and 2.8 mg/kg/day for females) for mice in the 78 week oncogenicity study with OMI-88 Technical. **Acceptable** (Pan, 5/3/11).

REPRODUCTION, RAT

** 53141-0120; 257046; "A Two-Generation Reproduction Toxicity Study of OMI-88 Technical in Rats"; (I. Matsuura *et. al.*; Kashima Laboratory, Mitsubishi Chemical Safety Institute Ltd., Kashima-gun, Ibaraki, Japan; Project ID. No. T-10022; 10/29/99); Thirty Sprague-Dawley rats/sex/group received 0, 0.75, 1.5 or 3.0 mg/kg/day of OMI-88 Technical (Tolfenpyrad Technical) (lot no. 6D-01-2; purity: 99.33%) in the diet for a 10-week premating period, mating, 3 weeks of gestation and 3 weeks of lactation. At the time of weaning, 24 F1 generation offspring/sex/group (except for the 3.0 mg/kg group for which only 22 animals/sex were selected) received the test material at the same treatment levels for a 10-week premating period (beginning post-weaning), mating, 3 weeks of gestation and 3 weeks of lactation. Three 3 mg/kg dams in the F0 generation died or were euthanized *in extremis* during parturition. In the F1 generation, one dam in the 1.5 mg/kg group died on day 13 of gestation. The mean body weight gains of both sexes in the 3 mg/kg parental groups of both generations were less than that of the control group over the course of the study (NS, $p<0.01$). The mean food consumption of these animals was likewise less than that of the control group. There was no apparent treatment-related effect upon the mating parameters of either generation. No treatment-related effect on the sperm count and their viability and degree of activity or the presence of abnormal sperm for the parental males in either generation was evident. There was no treatment-related difference in the ovarian follicle counts between the

control and 3 mg/kg dams of either generation. However, the gestation length was prolonged for the F0 dams in the 3 mg/kg group (p<0.01) and the size of the litters and pup viability prior to cull of the dams in the 3.0 mg/kg group, F0 generation, were less than that of the control group (p<0.05). These effects were not noted for the F1 generation. The mean 3 mg/kg pup weights of the F1 and F2 generations during the lactation period were less than those of the control group (p<0.01 or 0.05). Pinna unfolding was delayed for both sexes in the 3 mg/kg group for both generations (p<0.01). The time-to-eye-opening was delayed for the 3 mg/kg female pups in the F1 generation and for the 3 mg/kg male pups in the F2 generation (p<0.05). Acquisition of the surface righting reflex was delayed in the both sexes of the 3 mg/kg, F1 generation pups (NS, p<0.01). This effect was not evident in the F2 generation pups. The times to acquisition of the midair righting and the pupillary reflexes were not affected by the treatment. The time to the cleavage of the balanopreputial gland in F1 males and the time to vaginal opening in the F1 females was not affected by the treatment. Absolute and relative thymus weights were decreased in both sexes of the 3 mg/kg weanlings in the F1 generation and in the 0.75 mg/kg male weanlings and above and the 1.5 mg/kg female weanlings and above for the F2 generation (p<0.05 or 0.01). No histological lesions were noted in these thymuses. There was no apparent treatment-related effect upon organ weights of the parental animals in either generation. In the histological examination of the 3 mg/kg females of the F0 generation, hemorrhage (7/30), necrosis (4/30), inflammatory cell infiltration (5/30) and thrombus (3/30) were noted in the uteri. None of these lesions were evident in the uteri of the control group females. No treatment-related lesions were noted for the F1 parental generation. **No adverse effect indicated. Parental NOEL:** (M/F)1.5 mg/kg/day (based upon the lower body weight gain and food consumption noted for the parents in the 3.0 mg/kg group of both generations); **Reproductive NOEL:** (F) 1.5 mg/kg/day (based upon the lower gestation index and smaller mean litter size noted for the dams in the 3.0 mg/kg group of the F0 generation); **Developmental NOEL:** (M/F) 1.5 mg/kg/day (based upon the lower mean body weights and delayed acquisition of early developmental landmarks in the pups of both generations in the 3.0 mg/kg treatment group). **Study acceptable.** (Moore, 3/29/11)

Rat Preliminary Dose-Range Finding Reproduction Toxicity Study

53141-0119; 257045; “A Preliminary Reproduction Study of AP81088 in Rats”; (I. Matruura; Kashima Laboratory, Mitsubishi Chemical Safety Institute Ltd., Kashima-gun, Ibaraki, Japan; Project ID. No. T-10021; 7/3/96); Ten adult Sprague Dawley rats/sex/group were dosed with 0, 15, 50 or 100 ppm of AP81088 (Tolfenpyrad Technical) (lot no. P-1002; purity: 99.8%) in the diet for a 4-week premating period, a mating period, a 20-day gestation period and a 3-week lactation period (premating: (M) 0, 0.86, 2.73, 4.76 mg/kg/day, (F) 0, 0.92, 2.88, 4.38 mg/kg/day; gestation: (F) 0, 0.97, 3.07, 4.87 mg/kg/day; lactation: 0, 2.38, 7.35, 11.67 mg/kg/day). No parental deaths occurred during the study. The mean body weight gain of both sexes in the 50 and 100 ppm treatment groups was less than that of the control values during the premating period (NS, p<0.01 or 0.05). The mean food consumption of both sexes in the 50 and 100 mg/kg groups was less than that of the control group during the premating period. The fertility and gestation indices were not affected by the treatment. The number of total offspring/litter and offspring/litter which were born alive were reduced for the 100 mg/kg treatment group. During the lactation period, the mean body weight gain of the pups in the 50 and 100 mg/kg groups was less than that of the control group pups (p<0.01 or 0.05). No adverse effect evident. Parental NOEL: (M/F) 15 ppm ((M) 0.86 mg/kg/day, (F) 0.92 mg/kg/day) (based upon reduced body weight gain and food consumption for the parents in the 50 ppm treatment group); Reproduction NOEL: 100 ppm ((M) 4.76 mg/kg/day, (F) 4.38 mg/kg/day) (based upon the lack of a treatment-related effect on the 100 ppm treatment group); Developmental NOEL: 15 ppm ((F) 0.97 mg/kg/day) (based upon reduced body weight of the offspring in the 50 ppm treatment group); Study supplemental (dose range-finding study). (Moore, 3/21/11)

Rat Two Generation Immunotoxicity Study

** 53141-0143; 257089; "Next Generation Immunotoxicity Study of OMI-88 Technical in Rats"; (H. Atai, *et. al.*; Kashima Laboratory, Mitsubishi Chemical Safety Institute Ltd., Kashima-gun, Ibaraki, Japan; Project ID No. T10037; 10/29/99); Fifteen mated Sprague Dawley female rats/group received 0, 0.75 and 3.0 mg/kg/day of OMI-88 Technical (Tolfenpyrad Technical) (lot no. 6D-01-2; purity: 99.33%) in the diet for the 3-week gestation and lactation periods. Twelve offspring/sex/group from the F1 generation were selected and treated for 10 weeks (post-weaning) for the premating period, the mating period and for the 3-week gestation and lactation periods. An additional 18 male F1 offspring were selected for testing and maintained on study for the appropriate time intervals. Thirty males/group in the F2 generation received the same treatment levels for up to 7 weeks post-weaning. Thymus and spleens were weighed and the cellularity of both organs was determined for animals in the F1 and F2 generations. Specific surface markers on lymphocytes of the study animals were assessed at 4 and 21 days postnatal and for adult animals. Assays for humoral immune response and delayed hypersensitivity were included in the study. The mean body weight gain of the 3.0 mg/kg F0 dams was less than that of the control group during the gestation period ($p<0.01$). The mean food consumption of these dams was also less than the control group values during the gestation and lactation periods. These effects were not apparent for the F1 generation and for the males in the F2 generation. The mean litter size and viability index of the pups in the 3.0 mg/kg F1 generation was less than the control group values (NS, $p<0.01$). The body weight gain of the 3.0 mg/kg F1 generation pups was less than that of the control group during the lactation period ($p<0.01$ or 0.05). These effects were not so evident for the F2 generation (body weight gain of 3.0 mg/kg pups was slightly less (NS)). There was no apparent treatment-related effect upon the total and differential white blood cell counts of the F1 male weanlings and the F2 male weanlings and adult males. For the 4-day postnatal 0.75 mg/kg male offspring and for both sexes in the 3.0 mg/kg group of the F1 and F2 generations, the mean absolute and relative thymus and spleen weights were less than those of the control group (NS, $p<0.01$ or 0.05). By postnatal day 21, only the mean absolute and relative thymus weights of both sexes in the 3.0 mg/kg group of both generations were less than the control group values ($p<0.01$). For the adult males of both generations, no treatment-related effect on either organ was apparent. The total cell number and cellularity/g of tissue for the thymus and spleen in the 3.0 mg/kg group males were less than the control group values for the F2 4-day old pups and for the 21-day old weanlings of both generations ($p<0.01$ or 0.05). This effect was not evident for the F2 adult males. In the assay which evaluated the distribution of surface markers on the lymphocytes, the numbers of cells in the thymus and spleen possessing particular markers was lower for the 3 mg/kg F2 4-day old pups than for the control group ($p<0.01$ or 0.05). This lower number corresponded to the lower cellularity noted for these organs. The distribution of cell markers was not apparently affected by the treatment. In the humoral immune response, the anti-SRBC antibody titers of the F1 and F2 generation adult males was not affected by the treatment. In the delayed hypersensitivity assay, cell mediated immunity to KLH was not affected by the treatment in the F1 and F2 generation adult males. **No adverse effect was indicated. Rat immunotoxicity NOEL:** (M) 3.0 mg/kg/day (based upon the lack of a treatment-related effect at the 3.0 mg/kg treatment level). **Study acceptable.** (Moore, 4/3/11)

TERATOLOGY, RAT

** 53141-0110; 257014; "A Teratogenicity Study of OMI-88 Technical in Rats"; (Hoshino, N.; Kashima Laboratory, Mitsubishi Chemical Safety Institute Ltd., Kashima-gun, Ibaraki, Japan; Project ID. T-10024; 10/14/99); Twenty four mated female SD rats/group were dosed orally by gavage with 0 (vehicle: aqueous 0.5% sodium carboxymethyl cellulose) , 1, 3 or 4.5 mg/kg of OMI-88 Technical (Tolfenpyrad Technical) (lot no. 6D-01-2; purity: 99.33%) from day 6 through day 15 of gestation. No maternal deaths resulted from the treatment. The mean body weight gain and food consumption of the dams in the 3 and 4.5 mg/kg groups were less those of the control group

during the treatment period (p<0.05 or 0.01). The mean fetal weights of the male and female offspring of the 4.5 mg/kg group were less than the control values (p<0.05 or 0.01). There was no treatment-related increase in malformations or variations. **No adverse effect indicated. Maternal NOEL:** 1 mg/kg/day (based upon the lower body weight gain and food consumption of the dams in the 3 mg/kg group); **Developmental NOEL:** 3 mg/kg/day (based upon the lower fetal weights of the 4.5 mg/kg group); **Study acceptable.** (Moore, 3/15/11)

TERATOLOGY, RABBIT

** 53141-0112; 257016; "Teratogenicity Study of OMI-88 Technical in Rabbits"; (Fujii, O.; Kashima Laboratory, Mitsubishi Chemical Safety Institute Ltd., Kashima-gun, Ibaraki, Japan; Project ID No. T10030; 10/23/97); Sixteen artificially inseminated female Japanese white rabbits were dosed orally by gavage with 0 (vehicle: aqueous 0.5% sodium carboxymethylcellulose), 1, 3 or 6 mg/kg/day of OMI-88 Technical (Tolfenpyrad Technical) (lot no. 6D-01-2; purity: 99.33%) from gestation day 6 through gestation day 18. One doe in the 3 mg/kg group died on gestation day 28. The mean body weight gains of the 3 and 6 mg/kg does were less than that of the control animals over the course of the treatment period. The mean food consumption of these animals was less than that of the controls over the same time period. There was an increased number of fetuses in the 6 mg/kg group with a 13th rib (0: 13/84 vs 6: 33/71). **No adverse effects were indicated. Maternal NOEL:** 1 mg/kg/day (based upon the reduced body weight gain of the does in the 3 mg/kg group); **Developmental NOEL:** 3 mg/kg/day (based upon the increased incidence of a 13th rib among the fetuses in the 6 mg/kg group); **Study acceptable.** (Moore, 3/17/11)

<u>Rabbit Dose Range-Finding Teratology Study</u>

53141-0111; 257015; "A Preliminary Teratogenicity Study of AP81088 in Rabbits"; (I. Matsuura; Kashima Laboratory, Mitsubishi Chemical Safety Institute Ltd., Kashima-gun, Ibaraki, Japan; Project ID. No. T10029; 5/10/96); Eight artificially-inseminated female Japanese white rabbits/group were dosed orally by gavage with 0 (vehicle: aqueous 0.5% sodium carboxymethylcellulose), 1, 3, 6, or 9 mg/kg/day of AP81088 (Tolfenpyrad Technical) (lot no. P-1002; purity: 99.8%) from gestation day 6 through 18. One doe in the 9 mg/kg group died on day 22 of gestation. One doe in the 9 mg/kg group had no live fetuses. The mean body weight gain and food consumption of the 9 mg/kg group were less than the control values during the treatment period. The mean fetal body weights of the 9 mg/kg offspring were less than those of the control values. **No adverse effect indicated. Maternal NOEL:** 6 mg/kg/day (based upon the body weight loss and reduced food consumption noted for the does in the 9 mg/kg group); **Developmental NOEL:** 6 mg/kg/day (based upon the lower mean body weights of the fetuses in the 9 mg/kg group); **Study supplemental.** (Moore, 3/16/11)

GENE MUTATION

** 53141-0124; 257050; "OMI-88 Technical: Reverse Mutation in Five Histidine-Requiring Strains of *Salmonella typhmurium* and One Tryptophan-Requiring strain of *Escherichia coli*"; (M. Ballantyne; Covance Laboratories Limited, Harrogate, North Yorkshire HG3 1PY, England; Study No. 1509/1; 4/28/97); *S. typhimurium* strains TA98, TA100, TA102, TA1535, TA1537 and *E.coli* WP2 uvrA were treated with OMI-88 Technical (Tolfenpyrad Technical) (lot no. 6D-01-2; purity: 99.33%) at concentrations ranging from 8 to 5000 μg/plate for 48 to72 hours at 37° C under conditions of (+/-) activation in the 1st trial using the plate incorporation technique. In the 2nd trial, the strains were exposed to concentrations of the test material ranging from 62.5 to 1000 ug/plate under conditions of (+/-) activation. In the activated samples the cells were preincubated with the test material for 20 minutes followed by plating the cells. Each treatment level was plated in triplicate (5 plates for solvent control). An Aroclor 1254-induced rat liver S9 fraction was used to activate the test material. There was no apparent treatment-related increase in the incidence of reverse mutation.

The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 4/4/11)

** 53141-0126; 257065; "L5178Y $TK^{+/-}$ Mouse Lymphoma Forward Mutation Assay with a Confirmatory Assay"; (M. A. Cifone; Covance Laboratories Inc., Vienna, VA; Study No. 7883-100; 10/11/07); Mouse lymphoma L5178Y cells (clone 3.7.2C ($TK^{+/-}$)) were treated with Tolfenpyrad Technical (lot no. 365-65A; purity: 99.5%) at concentrations ranging from 0.01 to 75 ug/ml (non-activation) and 0.05 to 100 ug/ml (activation) in the first trial and from 0.005 to 10 ug/ml (non-activation) and 0.01 to 25 ug/ml (activation) in the second trial for 4 hours at 35 to 38° C. The vehicle control samples were incubated in triplicate. Single cultures were performed for each treatment level. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. The size of the mutant colonies was reported as a bimodal distribution. There was no treatment-related increase in the mutation frequency. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 4/6/11)

CHROMOSOME EFFECTS

**** 53141-0127; 257066**; "OMI-88 Technical: Induction of Chromosome Aberrations in Cultured Chinese Hamster Lung (CHL) Cells"; (S. Riley; Covance Laboratories Limited, Harrogate, North Yorkshire HG3 IPY, England; Study No. 1509/2; 5/27/97); Chinese hamster lung cell cultures were treated with concentrations of OMI-88 Technical (Tolfenpyrad Technical) (batch no. 6D-01-2; purity: 99.33%) ranging from 4.943 to 250 ug/ml under conditions of (+/-) activation in the 1st assay. Under conditions of non-activation, the cells were treated for 24 hours. In the activated treatments, the cells were treated for 6 hours and then incubated for an additional 18 hours. In the 2nd assay, under conditions of non-activation, the cells were treated with the test material at concentrations ranging from 8.59 to 51.2 ug/ml for 24 or 48 hours. An additional experiment was performed under conditions of non-activation in which the cells were exposed to concentrations ranging from 20.97 to 100.0 ug/ml of the test material for 6 hours and then incubated for an additional 18 hours. In the 2nd assay, cells were also treated under conditions of activation for 6 hours and then incubated for an additional 18 hours at concentrations ranging from 32.77 to 100 ug/ml. An Aroclor 1254-induced rat liver S9 fraction was used to activate the test material. Two cultures per treatment level were maintained. No treatment-related increase in cells with chromosomal aberrations was evident. However, there was an increase in the number of numerical aberrations (hyperdipliod, endoreduplicated, polyploid) under conditions of non-activation. This effect was more apparent as the treatment interval was increased. **Possible adverse effect:** increased incidence of numerical aberrations. Positive controls were functional for chromosomal aberrations. **Study acceptable.** (Moore, 4/8/11)

DNA DAMAGE

** 53141-0131; 257070; " *In Vivo* Mouse Bone Marrow Micronucleus Assay"; (Y. Xu; Covance Laboratories Inc., Vienna, VA; Study No. 7883-101; 10/12/07); At least five Crl:CD-1 (ICR) male mice/group were dosed orally twice in a 24-hour interval by gavage with 0 (vehicle: aqueous 0.5% carboxymethylcellulose), 5, 10, 20 or 50 (8 animals were dosed) mg/kg of Tolfenpyrad Technical (lot no. 365-65A; purity: 99.5%). Two animals in the 20 mg/kg group and 6 animals in the 50 mg/kg group died. The remaining two 50 mg/kg animals were dosed with 20 mg/kg on the 2nd day and included in that group (one of these died after the 2nd dose). All of the animals were euthanized at 24 hours post-final dose. A positive control group of 5 animals were treated by oral gavage with cyclophosphamide, 80 mg/kg (one dose) and was euthanized at 24 hours post-dose. Bone marrow samples from the tibia were examined and the ratio of polychromatic (PCE) to normochromatic erythrocytes (NCE) and the percentage of PCE with a micronucleus were determined. No treatment-related increase in the number of PCEs with a micronucleus was noted. The ratio of PCE to NCE was not significantly affected as well. The positive control was functional. **No adverse effect indicated. Study acceptable.** (Moore, 4/14/11)

NEUROTOXICITY

Rat Acute Neurotoxicity Study

0134; 257078; "Tolfenpyrad: Oral (Gavage) Acute Neurotoxicity Study in Crl:CD(SD) Rats" (Barnett, J. F., Charles River Laboratories, Horsham, PA, Study No. XTH00001, 05/02/2008). 870.62. Tolfenpyrad (Lot Number 365-65A, purity = 99.5%), suspended in corn oil, was administered in a single dose by gavage to 10 Crl:CD(SD) rats per sex per dose at dose levels of 0 (vehicle only), 10 (females only), 20, 40, and 60 (males only) mg/kg. No male mortalities occurred; one female at 40 mg/kg/day died on day 4 of the study. Clinical observations revealed treatment-related dehydration, scant feces, urine-stained abdominal fur, and soft or liquid feces in males at 60 mg/kg, and dehydration and urine-stained abdominal fur in females at 40 mg/kg . Treatment-related decreases in mean body weight and in mean feed consumption were observed in males at 40 and 60 mg/kg and in females at 20 and 40 mg/kg. During FOB assessments conducted on Day 1 (post-dose), treatment-related urine and/or fecal staining were observed in females at 40 mg/kg. Also, an increased (although not statistically significant) incidence in slight ataxic gait was observed in females at the 40 mg/kg dose during the Day 1 (post-dose) and Day 8 FOB assessments. Motor activity assessments revealed no treatment-related effects. Macroscopic and microscopic examinations of nervous system tissues revealed no treatment-related abnormalities. **No adverse effects.** NOEL (M) = 20 mg/kg and (F) = 10 mg/kg (based on decreased body weight and decreased feed consumption). **Acceptable.** (Corlett and Leung, 04/26/2011)

Rat Subchronic Neurotoxicity Study

53141-0133, 52843-0060, 53086-0145, -0146; 175277, 257077, 253819, 253821; "OMI-88 Technical Neurotoxicity Study by Dietary Administration to CD Rats for 13 Weeks" (Kilpatrick, H.C., Huntingdon Life Sciences Ltd., Huntingdon, Cambridgeshire, England, Project Identification: MUB 146/024442, 12/17/2003). 870.6200. OMI-88 Technical (Batch number 6D-01-2, purity = 99.33%) was admixed to the diet and fed to 10 Crl:CD(SD) IGS BR rats per sex per dose at dose levels of 0 (untreated diet), 15, 40, or 80 ppm (0, 1.0, 2.7, and 5.4 mg/kg/day, respectively, for males, and 0, 1.2, 3.2, and 6.0 mg/kg/day, respectively, for females) for 13 weeks. No mortalities occurred. No treatment-related clinical signs were observed. A treatment-related decrease in mean body weight gain in both sexes was observed at 80 ppm. During FOB assessments, a treatment-related decrease in body weight was observed at 80 ppm during weeks 2, 4, and 8 in males and during weeks 2, 4, 8, and 12 in females; no other treatment-related effects were observed during FOB assessments. Motor activity assessments revealed no treatment-related effects. No treatment-related effect on brain weight was observed. Macroscopic and microscopic examinations of nervous system tissues revealed no treatment-related abnormalities. **No adverse effects. NOEL (M)** = 2.7 mg/kg/day (40 ppm) and **NOEL (F)** = 3.2 mg/kg/day (40 ppm) based on decreased mean body weights during FOB assessments and decreased mean body weight gain. Study was previous deemed to be unacceptable but possibly upgradable with the submission of more recent positive control data from Huntingdon Life Sciences Ltd., Huntingdon, Cambridgeshire, England (the positive control data submitted in Document No. 53141-0135, Record No. 257081 were generated at another facility located at Eye Suffolk, England). The registrant has submitted additional positive control data which are sufficient to document the technical expertise of the staff performing the study (see discussion below). (Corlett and Leung, 05/05/11, upgraded Moore, 1/25/12)

MECHANISITIC STUDY

53141-0128; 257067; "Cell Cycle Kinetics in Chinese Hamster Lung (CHL) Cells"; (H. Murli; Covance Laboratories Inc., Vienna, VA; Study No. 7883-102; 9/28/07); Chinese hamster lung cell cultures were treated with concentrations of Tolfenpyrad Technical (lot no. 365-65A; purity: 99.5%) ranging from 5.00 to 15.0 ug/ml under the condition of non-activation. In the presence of BrdUrd, the cells were treated for 3, 6 or 24 hours and harvested after 24 hours of incubation. At 2 hours

prior to the harvest, Colcemid (0.1 ug/ml) was added. Replicate cultures per treatment level were maintained. In the treated cultures, the cell cycle was delayed in a dose-related manner with minimal dependence on exposure time. The delay in the cycle was comparable to that which was observed for the positive control. An increase in the incidence of polyploidy in comparison to the solvent, negative and positive controls was noted for all of the treatment levels at the 3 different treatment times (effect was marginal after exposure for 3 hours and marked after 6 and 24 hour exposures. **Possible adverse effect indicated. Study supplemental** (non-guideline study). (Moore, 4/12/11)

SUBCHRONIC TOXICITY STUDIES

Rat Subchronic Dietary Toxicity Study

53141-0099, 257003;" A 13-week subacute oral toxicity study of OMI-88 Technical in rats by dietary administration, followed by a 4-week recovery period "; Nishitomi, T., et al. 9/28/99. Kashima Laboratory, Mitsubishi Chemical Safety Institute Ltd., Ibaraki, Japan, Project ID: T-10012, 6L162. OMI-88 Technical (Lot No. 6D-01-2), 99.33% powder substance. Ten rats/sex/group were exposed in feed to OMI-88 Technical at 0, 15, 80 or 160 ppm [0.906, 4.78 or 9.33 mg/kg/day for the males, and 1.01, 5.17 or 9.32 mg/kg/day for the females] for a 13-week oral toxicity study. In addition, 6 rats/sex were included in the control group and high dose group for a 4-week recovery period. There was no mortality. No test substance related clinical signs were observed. Decreased body weight, body weight gains, and food consumption in the 160 ppm group rats was observed throughout the 4-week treatment period. Decreased food efficiency was observed from week 1 to 11. Similar trends were also observed in the 80 ppm group males and females during most weeks. In the 4-week recovery period, food consumption in the high-dose group was comparable to that of the control group, food efficiency and body weight gains were increased in the high-dose group males and females. Hematology and serum chemistry examinations revealed changes in a number of parameters in the high-dose males and females, among them the MCV, platelet, white blood cell, urea nitrogen, glucose, triglycerides, inorganic phosphorus and potassium. Some of these changes were also observed in the 80 ppm group rats. Decreased absolute organ weights and increased relative organ weights were observed in the brain, lungs, heart, liver, spleen, kidneys, adrenals and testes/ovaries at week 14. For the majority of these organs, the same trends continued in high-dose males and females at week 18. Increased relative weights of these organs were also observed in the 80 ppm group males and females at week 14. At final necropsy, small seminal vesicle, small prostate were observed in high-dose males, small ovary, small uterus and small vagina were observed in the high-dose females. Histological findings at week 14 included changes in mesenteric lymph node, bone barrow, submandibular gland, liver, pancreas, kidney, ovary, uterus and Harderian gland in high- and mid-dose animals. **NOEL**: 15 ppm OMI-88 (4.78 mg/kg/day for males and 5.17 mg/kg/day for females) for the 13-week oral toxicity study in rats due to changes in body weight, food consumption, clinical chemistry, necropsy and histological findings in the 80 ppm and 160 ppm group rats. **Acceptable** (Pan, 4/7/11).

Rat 21-Day Repeated Dosing Dermal Toxicity Study

53141-0105, 257009;" 21-Day Dermal Toxicity Study of Tolfenpyrad in Crl:CD(SD) Rats" Barnett, J., 5/2/08, Charles River Laboratories, Horsham, PA, Project ID: XTH00005. Tolfenpyrad (Lot No. 365-65A), 99.5% white crystalline powder. Ten rats/sex/group were exposed to Tolfenpyrad percutaneously at dosages of 0, 10, 50, or 200 mg/kg/day once daily for 6 hours per day for 21 continuous days. No test substance related mortality. One male rat in the 10 mg/kg/day dose group was sacrificed on day 21 due to broken palate. Increased incidence of grade 1 erythema and flaking were observed in the 50 and 200 mg/kg/day males and females, grade 1 flaking was also observed in 10 mg/kg/day males and females. Decreased body weight gain from day 1 to 21 was observed in the 50 and 100 mg/kg/day females. Statistically significant decrease of food consumption was

noted in 200 mg/kg/day females from day 15-21 and from day 1-21. In the final necropsy, pink mesentery was found in 4 males of 200 mg/kg/day group. Statistically significant increase of ratio of epididymides, testes, liver and heart to terminal body weight was observed in high dose males, increased ratio of liver and heart to terminal body weight was observed in high dose females. Hematology examinations revealed decreased white blood cells, absolute lymphocytes, absolute monocytes, and absolute eosinophiles in the 50 and 200 mg/kg/day males and high dose females. **Dermal Toxicity NOEL (No Observed Effect Level)**: < 10 mg/kg/day in rats in the 21-day dermal toxicity study due to the increased incidence of flaking in males and females. **Systemic Toxicity NOEL (No Observed Effect Level)**: 10 mg/kg/day due to female body weight and food consumption changes as well as hematological examination results in the males and females. No adverse effects. **Acceptable** (Pan, 4/26/11).

Rat 5-Day Repeated Inhalation Exposure Study

53141-0108, 257012;" Tolfenpyrad: Range-finding inhalation toxicity study in rats Supplement 1 to Tolfenpyrad: Four-week inhalation toxicity study in rats"; Arce, G., 9/14/10. E.I. du Pont de Nemours and Company, Newark, Delaware 19714, USA, Laboratory Project ID: DuPont-22217R Supplement to DuPont-22217 Nichino: T-10159. Tolfenpyrad, 99.5% pure white solid. Three male and three female rats were exposed to aerosols of Tolfenpyrad dust at 3.6, 26 or 79.3 mg/m^3 for a 5-day, 6-hour/day inhalation exposure. Death occurred on the first exposure day at the 26 (1M/1F) and 79.3 (2M2F) mg/m^3 groups and the exposure was stopped and the surviving rats were allowed to recover for a week. One week later, the 3.6 mg/m^3 group was continued and untreated rats were added to the experiment to be tested at 10.9 mg/m^3 (MMAN: 2.8um, GSD: 1.6) for an additional 4-day exposure. Surviving animals in all test groups gained weight at the end of the 22-day observation period. Chromodacryorrhea and lacrimation was observed in males and female rats from 3.6 mg/m^3 treatment group and males from 10.9 mg/m^3 group during exposure. Closed eyes were found in 3.6 and 10.9 mg/m^3 males and 26 and 79.3 mg/m^3 females during or post-exposure. Stained face was found in a female exposed to 79.3 mg/m^3 from days 2-5. Ataxia was observed in 1 female rat from 26 mg/m^3 exposure group on day 1 of exposure. Based on the result, 0.5, 2 and 10 mg/m^3 were chosen for the 4-week inhalation study. Supplemental Study. (Pan, 5/1/11)

Rat 4-Week Repeated Inhalation Exposure Study

53141-0109, 257013;" Tolfenpyrad: Four-week inhalation toxicity study in rats"; Kelly, D., 4/18/08. E.I. du Pont de Nemours and Company, Newark, Delaware 19714, USA, Laboratory Project ID: DuPont-22217. Tolfenpyrad, 99.5% pure white solid. Ten rats/sex/group were exposed nose-only to aerosols of Tolfenpyrad dust at 0, 0.50, 2.0 or 10 mg/m^3 (MMAD: 2.75, 2.95 and 3.2 um, respectively; GSD: 1.56, 1.6 and 1.65, respectively) for 6 hours/day, 20 exposures over a 4-week period. There was no mortality. No test substance related clinical signs, body weight, food consumption, and clinical chemistry changes were detected. Decreased absolute reticulocyte count was observed in the high males. Decreased white blood cell count and absolute lymphocyte count were observed in high dose females**.** Increased absolute and relative liver weight was observed in high dose females at final necropsy. Microscopically, increased liver hepatocellular hypertrophy was observed in high dose male (2/10) and female (3/10) rats. Increased kidney hyaline droplet was observed in 2 high dose males. **NOEL:** 2.0 mg**/**m^3 for repeated inhalation exposure to Tolfenpyrad dust in male and female rats. **No adverse effects. Acceptable** (Pan, 3/24/11).

Dog 4-Week Dietary Toxicity Study

53141-0104, 257008;" A 4-Week Oral Subacute Toxicity Study of OMI-88 Technical in Beagle Dogs (Dose Range Finding Study)" Nagashima, Y., 8/22/97, Bozo Research Center Inc., Setagaya-ku, Tokyo 156-0042, Japan, Project ID: T-10017. OMI-88 Technical (Lot No. 6D-01-2), 99.33% powder substance. Two Beagle dogs/sex/group were exposed to OMI-88 Technical at dietary levels of 0, 1, 5 or 10 mg/kg for a 4-week period. No mortality. Body weight loss and decreased food consumption

was noted in 1 male from 10 mg/kg dose group at weeks 3 and 4. Vomiting was noted in all treated dogs with increased incidence in mid and high dose dogs. Abnormalities in feces, (soft feces, watery feces or mucous feces) were observed with increased incidence in 5 mg/kg males and high dose males and females. Increased cytoplasmic eosinophilia in hepatocyte, swelling of distal tubular epithelium and vacuolation in collecting tubular epithelium in the kidney was observed in a 10 mg/kg male at pathological examination. **No Observed Effect Level (NOEL):** <1 mg/kg due to vomiting and soft feces (in males). The same dosage levels were selected for 13-week subacute oral toxicity study in Beagle Dogs. **Study supplemental**. (Pan, 4/21/11)

Dog Subchronic Dietary Toxicity Study

53141-0103, 257007;" A 13-Week Oral Subacute Toxicity Study of OMI-88 Technical In Beagle Dogs (A Supplementary Study)" Nagashima, Y., 3/30/99, The Third Laboratory for Safety Evaluation, Kannami Laboratory, Bozo Research Center Inc., Project ID: T-10019, BOZO/B-3644. OMI-88 Technical (Lot No. 6D-01-2), 99.33% powder substance. Four Beagle dogs/sex/group were exposed to OMI-88 Technical at dietary levels of 0, 10, 30, or 100 mg/kg for a 13-week period. Mortality: 1 male in the 30 mg/kg group, and all animals in the 100 mg/kg group died or were sacrificed moribund. Body weight loss was observed in the high-dose male and female dogs before they were dead or sacrificed moribund. Suppressed body weight gain was observed in the 30 mg/kg group male dogs in the second half of the study period. Decreased food consumption was observed in the high dose animals and 30 mg/kg group males in the second half of the study period. Increased incidence of vomiting and abnormalities of feces was observed in all test substance treated dogs. Increased incidence of salivation and emaciation was observed in the 30 and 100 mg/kg males, decrease in spontaneous movement, staggering gait, mydriasis, lateral position, miosis, hypothermia and prone position were also noted in the males died or sacrificed moribund. Increased salivation and estrus hemorrhage was observed in the 30 and 100 mg/kg females, emaciation, decrease in spontaneous movement, staggering gait, mydriasis, and watery feces were also noted in the females died or sacrificed moribund during the study. In the blood chemistry examinations, alkaline phosphatase and triglycerides were decreased at week 7 and 13 in test substance treated males and females, except for the alkaline phosphatase level in10 mg/kg females at week 13. Histological findings that were treatment related included changes in liver, lymph nodes, thymus, testis and prostate in the 30 and 100mg/kg group male dogs and the high-dose females. Changes in cerebrum, cerebellum and bone marrow were limited to the high-dose male and female dogs. **NOEL**: less than 10 mg/kg in Beagle Dogs in the 13-week subacute toxicity study due to the increased incidence of vomiting, abnormalities of feces and blood chemistry changes. **Acceptable** (Pan, 4/19/11).

Mouse 4-Week Dietary Toxicity Study

53141-0100, 257004;" A 4-week dietary range-finding study in mice with OMI-88 Technical"; Trutter, J. 4/10/99. Covance Laboratories, Project ID: T-10014. OMI-88 Technical (Lot No. 6D-01-2), 99.33% powder substance. Ten mice/sex/group were exposed to OMI-88 Technical at dietary levels of 0, 30, 100, 300, or 600 ppm [5.3, 17.5, 50.9, or 103.9 mg/kg/day for the males, and 6.5, 21.8, 67.2 or 126.2 mg/kg/day for the females] for a 4-week period. There was mortality at the high dose group only with 1 male and 2 females died or killed in moribund conditions. Clinical signs observed in the treated animals included cold to touch, hunched posture, thin appearance, ataxia, hypoactive, few feces, and rough haircoat in the high dose mice mostly. Decreased body weight, weight change and food consumption, increased relative liver weight at the final necropsy were noted in high dose mice as well as some 300 ppm group animals. NOEL: 100 ppm (17.5 mg/kg for male mice and 21.8 mg/kg for female mice) due to body weight change and relative liver weight increase in 300 and 600 ppm group mice. **No adverse effect; Acceptable** (Pan, 4/1/11).

Mouse Subchronic Dietary Toxicity Study

53141-0101, 257005;" 13-week dietary toxicity study in mice with OMI-88 Technical"; Trutter, J. 8/12/99. Covance Laboratories Inc., Vienna, Virginia 22182-1699, Laboratory Study ID: CHV 6287-104, T-10015. OMI-88 Technical (Lot No. 6D-01-2), 99.33% powder substance. Ten mice/sex/group were exposed to OMI-88 Technical at dietary levels of 0, 15, 100, or 300 ppm [2.4, 15.9 or 46.2 mg/kg/day for the males, and 3.0, 20.2, or 57.9 mg/kg/day for the females] for a 13-week period. Mean body weight and food consumption decrease was observed in high dose males throughout the study. Relative liver weight was increased in the high dose males and females at final necropsy without any treatment related histological change. **NOEL**: 100 ppm (15.9 mg/kg for male mice and 20.2 mg/kg for female mice) due to body weight change and relative liver weight increase in 300 ppm group mice. No adverse effects; **Acceptable** (Pan, 4/11/11).

METABOLISM STUDIES

Metabolism, Rat

53141-0140; 257086; "Fate of OMI-88 in Rats-Absorption, Distribution and Excretion by Repeated Oral Administration"; (M. Okada; Kashima Laboratory, Mitsubishi Chemical Safety Institute Ltd., Ibaraki, Japan; Study No. 8L127; 6/23/99); F344 rats of both sexes were treated with 1 mg/kg/day of Pyrazole-3-^{14}C-OMI-88 (lot no. CFQ9339B; specific radioactivity: 2.04 GBq/mmol; radiochemical purity: 99.5%) or Tolyl-U-^{14}C-OMI-88 (lot no. CFQ 9338B; specific radioactivity: 2.15 GBq/mmol, radiochemical purity: 99.5%) orally by gavage for 14 days. Pharmacokinetic parameters, an excretion profile and a time course of tissue distribution up to 168 hours post-dose were derived. In the pharmacokinetic evaluation, the concentration of radiolabel in the blood was determined during the treatment period and over a time-course of 168 hours post-final dose. The concentration of radiolabel in the blood reached a steady state level within the 1st week of treatment. The time to maximal concentration (tmax) was 8 hours for the males in both of the 1 mg/kg treatment groups and 12 hours for females in the 1 mg/kg group (Pyrazole-3-^{14}C-OMI-88). The $t_{1/2}$ values ranged from 18.6 to 20.7 hours for the males in the two treatment groups and 45.8 hours for the females in the 1 mg/kg group (Pyrazole-3-^{14}C-OMI-88). Radiolabel was predominantly recovered in the feces. Ninety two to 95% of the total administered dose was recovered in the feces across all of the treatment groups by 7 days post-final dose. At 4 hours post-final dose, the liver, kidneys, brown fat, fat, skin, stomach and small and large intestine were the tissues in which radiolabel was predominantly recovered. At 12 hours post-dose, the elevated levels of radioactivity persisted in these tissues. By 168 hours post-dose, the radioactivity persisted in the bone marrow, skin and fat while the levels in the other tissues demonstrated a significant decline. Radiolabeled residues were sequestered in these three tissues in the multiple dosing regimen with concentrations ten fold or greater at 168 hours post-final dose when compared to the results of the single dose regimen (study no. 7L365). **Study supplemental** (report does not include evaluation of the metabolites). (Moore, 4/25/11)

53141-0141; 257087; "Pharmacokinetic Study of OMI-88 in Rats-Absorption, Distribution and Excretion after a Single Oral Administration"; (M. Miyagawa; Kashima Laboratory, Mitsubishi Chemical Safety Institute Ltd., Ibaraki, Japan; Study No. 7L365; 3/17/98); F344 rats of both sexes were treated with either 1 or 20 mg/kg of Pyrazole-3-^{14}C-OMI-88 (lot no. CFQ9339A; specific radioactivity: 2.04 GBq/mmol; radiochemical purity: 99.7%) or Tolyl-U-^{14}C-OMI-88 (lot no. CFQ 9338A; specific radioactivity: 2.15 GBq/mmol, radiochemical purity: 99.5%) orally by gavage. Pharmacokinetic parameters, an excretion profile (including biliary excretion) and a time course of tissue distribution up to 168 hours post-dose were derived. In the pharmacokinetic evaluation, the concentration of radiolabel in the blood was determined over a time-course of 168 hours post-dose. The time to maximal concentration (tmax) varied from 2 to 4 hours for the males in both of the 1 mg/kg treatment groups to 12 hours for both males and females in the 20 mg/kg group

(Pyrazole-3-^{14}C-OMI-88). The $t_{1/2}$ values ranged from 14.2 to 27.6 hours for the Pyrazole-3-^{14}C-OMI-88-treated animals and from 11.0 to 12.6 hours for the Tolyl-U-^{14}C-OMI-88-treated animals. Radiolabel was predominantly recovered in the feces, being excreted via the bile. Eighty eight to 93% of the administered dose was recovered in the feces across all of the treatment groups by 7 days post-dose. In the bile duct cannulation study, 64 and 55% of the administered dose was recovered in the bile of the males and females in the 1 mg/kg group and 70 and 51% of the dose was recovered in the bile of the males and females in the 20 mg/kg treatment group, respectively, by 48 hours post-dose. Absorption of the test material was 80 and 86% for the males in the 1 and 20 mg/kg groups and 76 and 61% for the females in the 1 and 20 mg/kg groups, respectively, by 48 hours post-dose. Fifty five to 85% of the administered dose was excreted by 48 hours post-dose. At 4 or 6 hours post-dose, the liver, kidneys, brown fat, stomach and small intestine were the predominant tissues in which radiolabel was recovered. At 12 or 24 hours post-dose, the elevated levels of radioactivity persisted in these tissues as well as in the large intestine. By 168 hours post-dose, the radioactivity persisted in the bone marrow, skin and fat while the levels in the other tissues demonstrated a significant decline. **Study supplemental** (report does not include evaluation of the metabolites). (Moore, 4/20/11)

53141-0138; 257084; “Fate of OMI-88 in Rats-Metabolism after a Single Oral Administration’; (T. Nishitomi; Kashima Laboratory, Mitsubishi Chemical Safety Institute Ltd., Ibaraki, Japan; Study No. 7L366; 7/13/99); Radiolabeled compounds recovered in Study No. 7L365 (see vol. no. 53141-0141, rec. no. 257087). F344 rats of both sexes were treated with either 1 or 20 mg/kg of Pyrazole-3-^{14}C-OMI-88 (lot no. CFQ9339A; specific radioactivity: 2.04 GBq/mmol; radiochemical purity: 99.7%) or Tolyl-U-^{14}C-OMI-88 (lot no. CFQ 9338A; specific radioactivity: 2.15 GBq/mmol, radiochemical purity: 99.5%) orally by gavage. Urine, fecal and bile samples recovered up to 48 hours post-dose were analyzed by HPLC equipped with a radioisotope detector. Retention times were compared to known standards. The primary route of excretion was via the feces which constituted as much as 98% of the recovered radiolabel during the 1st 48 hours post-dose. The primary metabolic pathway was oxidation of the tolyl methyl group to the carboxylic acid. The carboxyl group was then conjugated with glucuronic acid or tauric acid. The benzoic acid derivative and/or its conjugated moiety constituted 61 to 70% of the radiolabel recovered in the bile. Unmetabolized parent compound was recovered in the feces, particularly during the 1st 24 hours post-dose. In the bile-duct cannulation study, the parent compound constituted 73 to 84% of the radiolabel recovered in the feces with the remainder being the benzoic acid derivative. The benzoic acid derivative was the primary metabolite recovered in the plasma, liver, kidneys and fat. **Study supplemental.** (Moore, 4/21/11)

53141-0137; 257083; “Fate of OMI-88 in Rats-Preliminary Study”; (M. Okada; Kashima Laboratory, Mitsubishi Chemical Safety Institute Ltd., Kashima-Gun, Ibaraki, Japan; Study No. 6L190; 2/4/97); A limited number of male and female F344 rats were dosed orally with 2 or 20 mg/kg of Tolyl-U-^{14}C-OMI-88 (lot no. CFQ 9338; specific radioactivity: 2.15 Gbq/mmol, radiochemical purity: 99.0%) or Pyrazole-3-^{14}C-OMI-88 (lot no. CFQ9339; specific radioactivity: 2.04 Gbq/mmol; radiochemical purity: 99.6%) in a preliminary rat metabolism study. The excretion profile (including the biliary pathway), blood levels, and residual tissue levels of radioactivity were evaluated. The time-to-peak maximal concentration in the blood (Cmax) ranged between 3 and 10 hours post-dose, depending on the sex and dose level. Excretion was predominantly via the feces (92 to 94% of the administered dose). In the bile duct cannulation study, 22 to 35% of the dose was recovered from the bile up to 48 hours post-dose, depending on the position of the radiolabel. Recovery of radiolabel in the expired air was negligible. The tissues with the greatest concentration of radiolabel were the liver, fat and brown fat, bone marrow (particularly females), and to a lesser extent the kidneys and skin. Based on the percentage of dose administered, the liver and the contents in the large intestines had the greatest amount of radiolabeled test material at 96

hours post-dose. Although the presence of metabolites in the urine and feces was investigated, no quantitative data was presented in the report. **Study supplemental** (the study was a preliminary rat metabolism study). (Moore, 4/15/11)

STUDIES ON METABOLITES

Acute Oral Toxicity

0092; 256996; "Acute Oral Toxicity Study of OH-PT in Rats" (Ikeya, M., Bozo Research Center, Inc., Gotemba Laboratory, Japan, Study Number B-4162, 01/12/1999). 870.11. OH-PT (Lot number Y980423, purity = 99.9%, a metabolite of the active ingredient) was suspended in 0.5% w/v CMC-Na solution and administered in a single dose by gavage to 5 Sprague-Dawley (Crj:CD(SD)) rats per sex per dose at dose levels of 0 (vehicle only), 10, 30, 100, 300, and 1000 mg/kg. Mortalities occurred as follows- males: 0/5, 0/5, 1/5, 5/5, 3/5, 5/5, respectively; females: 0/5, 0/5, 3/5, 5/5, 4/5, 5/5, respectively. No clinical signs were observed in either sex at 10 mg/kg. At 30 mg/kg and above clinical signs were observed including decrease in spontaneous movement, animals in prone position, oligopnea, deep breathing, dyspnea, and diarrhea with all signs clearing in the surviving animals within 1 day of dose administration. Necropsy revealed no abnormalities. NOEL (M/F) = 10 mg/kg (no clinical signs). LD_{50} (M) = 70.8 (34.7-144.5) mg/kg, LD_{50} (F) = 35.5 (17.4-72.4) mg/kg, LD_{50} (M/F) = 50.1 (30.3-83.0) mg/kg. Toxicity Category I. **Supplemental study** (test article is a metabolite of the active ingredient tolfenpyrad) (Corlett, 03/23/2011)

Mutagencitiy

** 53141-0125; 257052; "A Reverse Mutation Test of OH-PT Using Bacteria"; (M. Ozaki; Bozo Research Center Inc., Gotemba Laboratory, Japan; Study No. M-1016; 2/18/99): In the dose range-finding assay, *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and *E.coli* WP2 uvrA were treated with OH-PT (tolfenpyrad metabolite) (lot no. Y980423; purity: 99.9%) at concentrations ranging from 0.305 to 5000 μg/plate for a 20-minute preincubation period, followed by 48 hours at 37° C, using the plate incorporation method, under conditions of (+/-) activation. In the main test, the strains were exposed to concentrations of the test material ranging from 2.44 up to 5000 ug/plate under the same conditions. Each treatment level was plated in triplicate. A phenobartibal/5,6-benzoflavone-induced rat liver S9 fraction was used to activate the test material. There was no apparent treatment-related increase in the incidence of reverse mutation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 4/5/11)

Chromosome Effects

** 53141-0129; 257068; "A Chromosomal Aberration Test of OH-PT Using CHL Cells"; (M. Ozaki; Bozo Research Center Inc., Gotemba Laboratory, Japan; Study No. M-1090; 1/5/01); Chinese hamster lung fibroblast cell cultures (CHL/IU) were treated with concentrations of OH-PT (metabolite of tolfenpyrad) (lot no. Y980423; purity: 99.9%) ranging from 40 to 200 ug/ml under conditions of (+/-) activation for 6 hours, followed by an additional 18 hours of incubation. In addition, the cells were exposed to concentrations of the test material ranging from 10 to 130 ug/ml for 24 or 48 hours without activation. A phenobartibal/5,6-benzoflavone-induced rat liver S9 fraction was used for activation. At least two cultures per treatment level were maintained. No treatment-related increase in number of cells with chromosomal or numerical aberrations (polyploidy) was evident. **No adverse effect indicated.** Positive controls were functional. **Study acceptable.** (Moore, 4/13/11)

DNA Damage

** 53141-0130; 257069; "A Micronucleus Test of OH-PT in Rats"; (K. Saigo; Safety Research Facility, Shin Nippon Biomedical Laboratories, Ltd., Japan; Study No. SBL 92-14; 12/28/00); Six male Sprague-Dawley rats/group were dosed twice in a 24-hour interval with 0 (vehicle: aqueous

0.5% carboxymethylcellulose), 5, 10 or 20 mg/kg of OH-PT (metabolite of tolfenpyrad) (lot no. Y000328; purity: 99.9%). The highest dose approximated the rat oral LD50 value. At 24 hours post-final dose, the bone marrow in the femurs of each animal was recovered and the percentages of micronucleated immature erythrocytes/immature erythrocytes/animal and immature erythrocytes/total erythrocytes (immature and mature)/animal were determined. There was no treatment-related increase in the percentage of micronucleated immature erythrocytes. There was a dose-related reduction in the percentage of immature erythrocytes at all of the treatment levels ($p<0.05$). **No adverse effect indicated.** The positive control was functional. **Study acceptable.** (Moore, 4/13/11)