CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Indaziflam

Chemical Code #5999 , **Tolerance** # 53082
SB 950 # New A.I.

10/28/09

I. DATA GAP STATUS

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

* Adverse effect was not oncogenic.

Toxicology one-liners are attached.

All record numbers through #248891 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T091028
Revised by TMoore, 10/28/09

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

COMBINED, RAT

**** 53082-0242; 248890**; "Chronic Toxicity and Carcinogeneity Study of BCS-AA10717 in the Wistar Rat by Dietary Administration"; (C. Langrand-Lerche; Bayer CropScience, BP 153, 06903 Sophia Antipolis Codex, France; Study No. SA 05251; 2/27/09); Sixty Wistar rats/sex/group received 0, 300, 3000 or 10000 ppm of Technical Grade BCS-AA10717 (lot no. EFIM000511; purity: 93.14%) in the diet for two years. An additional 10 animals/sex/group received the same treatment for 12 months. The treatment level of the 10000 ppm females was reduced to 6000 ppm on study day 281 because of the severity of the clinical signs experienced by these animals. Uptake of the active ingredient was as follows: (M) 0, 12, 118, and 414 mg/kg/day, (F) 0, 17, 167, 661 (weeks 0 to 40), 452 mg/kg/day (overall). During the first 40 weeks of the study, the females in the 10000 ppm group demonstrated treatment-related signs of tremors, dilated pupils, limited use of limbs, uncoordinated movements, splayed hindlimbs, labored and/or noisy respiration and anogenital soiling. After the reduction of the treatment level to 6000 ppm, these signs were still apparent for these females. The males in the 10000 ppm group also displayed some of these signs as well but were less affected. The mean body weights of both sexes in the high dose group were less than the control values throughout the study ($p<0.01$ or 0.05). Mean food consumption for the males in the 10000 ppm group was less than that of the control group during the first 2 weeks of the study ($p<0.01$ or 0.05). Thereafter no difference in consumption was apparent. For the females in the 10000 ppm group, food consumption was less than that of the control group during the 1st two months of the study. Thereafter, the consumption by this group was comparable to the control group values. No treatment-related effect was noted in the hematology. The urinalysis parameters were not affected in a dose-related manner over the course of the study. The T3, T4 and TSH values were not affected by the treatment after 3 or 14 weeks of treatment. In the clinical chemistry evaluation, the mean serum cholesterol and triglyceride levels of the high dose females were elevated during the first 6 months ($p<0.01$). Thereafter, no effect was apparent. The mean serum total protein and albumin levels of the high dose females were less than those values of the control group during the first 12 months of treatment ($p<0.01$ or 0.05).. Thereafter no effect was apparent. The mean serum phosphate levels of both sexes in the high dose group were greater than the control group values during the 1st 12 months of treatment ($p<0.01$ or 0.05). Thereafter, no effect was apparent. In the ophthalmology examination, absence of a pupillary reflex and dilatation of the pupil was noted for females in the high dose group after 12 months of treatment. These effects were not evident at the termination of the study. In the necropsy examination, the mean relative liver weights of the 3000 and 10000 ppm males after 12 months of treatment and of both sexes in the high dose group after 24 months of treatment were greater than the control group values ($p<0.01$ or 0.05). The mean relative kidney weights of both sexes in the high dose group were greater than those of the control group after 24 months of treatment ($p<0.01$ or 0.05). The mean absolute and relative epididymis weights and the mean relative testis weight of the 10000 ppm males were greater than the control values after 12 months ($p<0.01$ or 0.05). These effects were not apparent after 24 months of treatment. In the histopathology, vacuolation in the median eminence of the brain was noted for both sexes of the high dose group ((M) 0: 0/60 vs. 10000: 3/60, (F) 0: 0/60 vs. 6000: 4/60). Peripheral bilateral retinal atrophy was observed in the eyes of both sexes in the high dose group ((M) 0: 1/59 vs, 10000: 4/60, (F) 0: 3/60 vs. 6000: 16/60). Localized retinal atrophy, focal/multifocal, was also apparent in the eyes of five females in the 6000 ppm group. In the liver, centrilobular to panlobular hepatocellular hypertrophy was evident for both sexes in the intermediate and high dose treatment groups ((M) 0: 0/60 vs. 3000: 15/60, 10000: 33/60, (F) 0: 0/60 vs. 3000: 19/60, 6000: 39/60). Hepatocellular centrilobular vacuolation was also evident in the livers of the 10000 ppm males and the 3000 and 6000 ppm females ((M) 0: 0/60 vs. 10000: 17/60, (F) 0: 0/60 vs. 3000: 9/60, 6000: 13/60). An increased incidence of hepatocellular single cell necrosis was noted for the 3000 and 6000 ppm females (0: 2/60 vs. 3000: 5/60, 6000: 9/60). Hepatocytic brown pigment was also evident in a majority of the 6000 ppm females. In the pituitary gland, vacuolation of the pars nervosa was noted for both sexes in the intermediate and high dose groups ((M) 0: 1/60 vs. 3000: 3/60, 16/60, (F) 0: 0/59 vs. 3000: 4/59, 6000: 23/60).

Possible adverse effects: tremors, retinal atrophy and hepatic necrosis; **Rat Chronic Dietary Toxicity NOEL:** (M/F) 300 ppm (M) 12 mg/kg/day, (F) 17 mg/kg/day) (based upon the treatment-related effects noted in the livers of both sexes in the 3000 ppm group); **oncogenicity not apparent; Study acceptable.** (Moore, 9/24/09)

CHRONIC TOXICITY, RAT

See Combined, Rat above.

CHRONIC TOXICITY, DOG

**** 53082-0208, -0209; 243611, 243612**; "A One Year Toxicity Feeding Study in the Beagle Dog with Technical Grade BCS-AA10717'; (D.A. Eigenberg; Bayer CropScience LP, Toxicology, Stilwell, KS; Report No. 201740; 7/1/08); Four beagle dogs/sex/group received 0, 60, 225 or 450 ppm of Technical Grade BCS-AA10717 (lot no. EFIM000511; purity: 93.14% (analyzed 11/07)) for 1 year ((M) 0, 2, 6, and 12 mg/kg/day; (F) 0, 2, 7, and 11 mg/kg/day). One male in the 450 ppm treatment group was euthanized *in extremis* on study day 190 after suffering seizures. The mean body weight gains of both sexes in the 450 ppm group were less than the control values throughout most of the study, particularly in the early months. The mean food consumption of both sexes in the 450 ppm group was less than that of the control group throughout the study. The ophthalmology, hematology and neurological examinations did not reveal any treatment-related effects. In the clinical chemistry evaluation, the serum glucose levels for both sexes in the 450 ppm group were greater than the control levels at various times during the study (NS, $p<0.05$). However, the values did not represent a toxicological effect. In the urinalysis, the urinary ketones of both sexes in the 450 ppm group were elevated at various times during the study. However, no consistent effect was apparent. No treatment-related effects were noted in the necropsy examination. In the histopathological evaluation, axonal degeneration was noted in the spinal cord of both sexes in the 225 and 450 ppm groups ((M) 0: 0/4 vs. 225: 3/4 (severity: 1.0), 450: 3/4 (2.0), (F) 0: 0/4 vs. 225: 1/4 (severity: 2.0), 450: 4/4 (severity: 2.8). **Possible adverse effect:** axonal degeneration in the spinal cord**. Dog Chronic Dietary Toxicity NOEL:** (M/F) 60 ppm (M/F: 2 mg/kg/day) (based upon axonal degeneration in the spinal cord of both sexes in the 225 ppm group)**. Study acceptable.** (Moore, 9/16/09)

ONCOGENICITY, RAT

See Combined, Rat above.

ONCOGENICITY, MOUSE

**** 53082-0241; 248889**; "BCS-AA10717: Carcinogeneity Study in the C57BL/6J Mouse by Dietary Administration"; (P. Kennel; Bayer CropScience, BP 153, 06903 Sophia Antipolis Codex, France; Study No. SA 05252; 12/11/08); Fifty C57BL/6J mice/sex/group received 0, 50, 250 or 1000 ppm of Technical Grade BCS-AA10717 (lot no. EFIM000511; purity: 93.14%) in the diet for 18 months ((M) 0, 6.8. 34, 142 mg/kg/day, (F) 0, 8.4, 42, 168 mg/kg/day). An additional 10 animals/sex/group were euthanized after 12 months of treatment. There was no treatment-related effect upon the survival of the study animals. The mean body weights and food consumption of both sexes in the 1000 ppm group were less than the control values over the course of the study ($p<0.01$). In the hematology evaluation, the red blood cell count, the hemoglobin concentration and the hematocrit of the 1000 ppm males were less than the control values after 12 months of treatment ($p<0.01$ or 0.05). However, no effect was apparent on these parameters after 18 months of treatment. The mean absolute and relative kidneys weights of both sexes in the 1000 ppm group were less than the control values after both 12 and 18 months of treatment ($p<0.01$). The absolute and relative liver weights of the 1000 ppm females were less than the control values after 18 months of treatment ($p<0.01$). In the histopathological evaluation, collecting duct hyperplasia, pelvic epithelium hyperplasia, papillary necrosis and intratubular yellow brown material were noted in the kidneys of the 1000 ppm males ($p<0.01$). An increased incidence of centrilobular hepatocellular vacuolation was noted in the livers of both sexes in the 1000 ppm group ($p<0.01$). Glandular erosion/necrosis was noted in the stomachs of the 1000 ppm females ($p<0.01$). Eosinophilic cytoplasmic alteration was evident in the gallbladders of the 1000 ppm females, as well ($p<0.01$). **Possible adverse effect:** papillary necrosis in the kidney; **Mouse Chronic Dietary Toxicity NOEL:** (M/F) 250 ppm ((M) 34 mg/kg/day, (F) 42 mg/kg/day)

(based upon the lower mean body weights and the incidence of lesions in the kidneys, liver, stomach and/or gallbladder of both sexes in the 1000 ppm group); **No oncogenicity was evident. Study acceptable.** (Moore, 9/17/09)

REPRODUCTION, RAT

** 53082-0207; 243610; "Technical Grade BCS-AA10717: A Two Generation Reproductive Toxicity Study in the Wistar Rat"; (A.D. Milius, B.P. Stuart, S.G. Lake; Bayer CropScience LP, Toxicology, Stilwell, KS; Report No. 201883; 7/1/08); Thirty rats/sex/group in the P generation received 0, 100, 1000, or 8000 ppm of Technical Grade BCS-AA10717 (lot no. EFIM000511; purity: 93.14% (analyzed 11/07)) in the diet for a 10-week premating period, up to 2 weeks during the mating period and for 3 weeks both for the gestation and lactation periods. At that time, the concentration of the test material in the diet of the high dose group was reduced to 4000 ppm due to the severity of the clinical signs exhibited by the high dose F1 pups. The 30 F1 animals/sex/group which were selected as parents, were treated for 10 weeks during the premating period, followed by mating and 3 weeks each for gestation and lactation of the F2 generation (P generation: (M) 0, 10.2, 68.9, 560.1 mg/kg/day, (F) 0, 12.6, 83.2, 656.2 mg/kg/day, F1 generation: (M) 0, 10.6, 69.6, 317.6 mg/kg/day, (F) 0, 13.1, 87.2, 355.5 mg/kg/day). Parents in the 8000 ppm group had lower mean body weight gain than the control animals over the course of the study (NS, $p<0.05$ or 0.01). The F1 parental females in the 1000 and 4000 ppm groups had lower mean body weight gains than the control animals during the gestation period ($p<0.01$ or 0.05). The high dose females also demonstrated a lower mean body weight during the lactation period ($p<0.01$). The mean food consumption of the 8000 ppm females was less than that of the control females in the P generation (NS, $p<0.01$). Likewise, the mean food consumption of the F1 dams in the 4000 ppm group was less than the control animals over the course of the treatment (NS, $p<0.01$). No treatment-related effect was noted for the mating parameters. The mean litter size of the F1 generation dams in the 4000 ppm group was less than that of the control group. The mean F1 pup weights in the 8000 ppm group were less than the control values over the course of the lactation period ($p<0.01$). The mean F2 pup weights of the 1000 and 4000 ppm groups were marginally less than those of the control group by the end of the lactation period (NS, $p<0.05$). Pup viability was not apparently affected up through the end of the lactation period in either generation. Pups in the high dose group of the F1 generation, between post-natal days 22 and 61 and prior to the reduction of the dose from 8000 to 4000 ppm, were severely affected by the treatment. Two pups were euthanized *in extremis* on day 23 and two other pups were found dead on day 27. Other pups in the group exhibited increased activity, increased reactivity, myoclonic convulsions, tremors, labored breathing, diarrhea and soft stools. In the necropsy examination of the P generation, the mean absolute and relative liver weights of the1000 and 8000 ppm males and the mean relative liver weights of the 8000 ppm females were greater than the values of the control animals ($p<0.05$). In the F1 generation, the mean relative liver weights of both sexes in the 4000 ppm group were greater than those of the control group ($p<0.05$). The mean absolute and relative spleen weight of 21-day old pups (both sexes) in the high dose groups of both generations were less than the control values ($p<0.01$). No treatment-related effect was noted for the time to vaginal opening and ovarian follicle counts of the F1 female offspring or on preputial separation of the adult F1 males. The spermatogenesis in the adult males of both generations was not affected. In the histopathological examination, hyaline degeneration and tubular regeneration were noted in the kidneys of the P generation males in the 8000 ppm group and hyaline degeneration alone in the kidneys of the 4000 ppm F1 parental males. Liver hypertrophy was evident in the livers of both sexes in the high dose groups of both generations. Vacuolation was noted in the adrenal glands of the 8000 ppm females in the parental generation. **No adverse effects indicated. Parental NOEL:** 150 ppm (based upon increased liver weight and lower mean body weight gain noted for males and females, respectively, in the 1000 ppm group, (M) 10.2 mg/kg/day, (F) 12.6 mg/kg/day); **Reproductive NOEL:** 1000 ppm ((M) 68.9 mg/kg/day, (F) 83.2 mg/kg/day) (based upon the lower mean litter size noted for the 4000 ppm group in the F2 generation); **Developmental NOEL:** 150 ppm (based upon lower mean pup weights in the 1000 ppm group during the lactation period of both generations, (F) 12.6 mg/kg/day); **Study acceptable.** (Moore, 9/14/09)

53082-0186; 243589; "Technical Grade BCS-AA10717: A Dose Range-Finding Reproductive Toxicity Study in Wistar Rats"; (A.D. Milius, H. Hoss; Bayer CropScience LP, Toxicology, Stilwell, KS; Report No. 201879; Ten Wistar rats/sex/group received 0, 200, 1000, 3000 or 8000 ppm of BCS-AA10717 (batch no. EFIM000511; purity: 93.14%) in the diet for 10 weeks during the premating period, the 7-day mating period and during the gestation and lactation periods. The treatment levels were adjusted to 0, 100, 500, 1500 and 4000 ppm during the lactation period in order to compensate for the increased food consumption during this period. Compound uptake was reported to be 0, 12.7, 60.9, 188.7 and 514.9 mg/kg/day for the males and 0, 14.3 to 15.6, 71.9 to 76.8, 202.7 to 248.8 and 545.7 to 616.4 mg/kg/day for the females during the premating, gestation and lactation periods. No parental deaths occurred during the study. The mean body weight gain of the 8000 ppm females was less than that of the control group during the premating and gestation periods (NS or p<0.01). The mean food consumption of these females was less than that of the control group during the premating period (NS). The body weight gain and food consumption of the parental males were not affected by the treatment. No treatment-related effect was noted on the mating parameters. The mean litter size of the 8000 ppm treatment group was less than that of the control group. The mean body weights of the F1 pups was less than that of the control group by end of the lactation period. There was no treatment-related effect upon pup viability. **No adverse effect indicated. Study supplemental** (not a guideline study). (Moore, 8/18/09)

TERATOLOGY, RAT

** 53082-0180; 243583; "AE 1170437: Developmental Toxicity Study in the Rat by Gavage"; (S. Wason; Bayer CropScience, BP 153, 06903 Sophia Antipolis Codex, France; Study No. SA 06012; 10/27/06); Twenty three mated female Sprague-Dawley rats were dosed orally by gavage with 0 (vehicle: aqueous 0.5% methylcellulose 400), 10, 25 or 200 mg/kg/day of AE 1170437 Technical (batch no. EFIM000511; purity: 94.5%) from gestation day 6 through gestation day 20. One dam in the 200 mg/kg group was found dead on day 9 as a possible consequence of a dosing error. The mean body weight gain and food consumption of the 200 mg/kg dams was less than that of the control group over the course of the treatment period (NS, p<0.05). The mean fetal weights of the 200 mg/kg group were less than that of the control group (p<0.01). No other developmental effects were noted. **No adverse effect indicated. Maternal NOEL:** 25 mg/kg/day (based upon lower mean body weight gain and food consumption noted for the 200 mg/kg dams); **Developmental NOEL:** 25 mg/kg/day (based upon the lower mean fetal weight for the 200 mg/kg group); **Study acceptable.** (Moore, 7/31/09)

TERATOLOGY, RABBIT

** 53082-0181; 243584; "BCS-AA10717: Developmental Toxicity Study in the Rabbit by Gavage"; (S. Wason; Bayer CropScience, BP 153, 06903 Sophia Antipolis Codex, France; Study No. SA 07017; 1/31/08); Twenty three mated female New Zealand White rabbits/group were dosed orally by gavage with 0 (vehicle: aqueous 0.5% methylcellulose 400), 10, 25 or 60 mg/kg/day of BCS-AA10717 (previously referred to as AE 1170437) (batch no. EFIM000511; purity: 93.14%) from gestation day 6 through gestation day 28. One doe each in the control and 10 mg/kg groups were euthanized on day 21and 12, respectively, due to possible gavage error. Another female in the 10 mg/kg group was euthanized for humane reasons on day 22 due to significant body weight loss and one doe in the 60 mg/kg group was euthanized on day 27 after she aborted. The mean body weight gain and food consumption of the 60 mg/kg females were less than the control values over the course of the treatment (p<0.01 or 0.05). No treatment-related effects upon the development of the fetuses were evident. **No adverse effect indicated. Maternal NOEL:** 25 mg/kg/day (based upon lower body weight gain and food consumption for the 60 mg/kg does); **Developmental NOEL:** 60 mg/kg/day (based upon the lack of treatment-related effects on the 60 mg/kg fetuses); **Study acceptable.** (Moore, 8/10/09)

GENE MUTATION

** 53082-0194; 243597; "*Salmonella*/Microsome Test: Plate Incorporation and Preincubation Method"; (B. Herbold; Bayer HealthCare AG, PH-GDD Toxicology, 42096 Wuppertal, Germany; Study No. T 3076145; 8/30/06); *S. typhimurium* TA98, TA100, TA102, TA1535 and TA1537 strains were incubated with AE 1170437 technical (batch no. EFIM000511; purity: 90.32%) at levels ranging from 16 to 5000 µg/plate (both trials) under conditions of (-/+) activation and

incubated for 48 hours at 37° C by means of the plate incorporation method. In the 2nd trial, the bacterial strains were preincubated with the test material for 20 minutes prior to incorporation into the agar. Each treatment was incubated in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 8/18/09)

** 53082-0197; 243600; "*Salmonella*/Microsome Test: Plate Incorporation and Preincubation Method"; (B. Herbold; Bayer HealthCare AG, BSP-GDD-GED-GTOX Genetic Toxicology, 42096 Wuppertal, Germany; Study No. T0077781; 12/3/07); *S. typhimurium* TA98, TA100, TA102, TA1535 and TA1537 strains were incubated with AE 1170437 (batch no. 2007-007387; purity: 95.7%) at levels ranging from 16 to 5000 µg/plate in the 1st trial and from 100 to 3200 ug/plate in the 2nd trial under conditions of (-/+) activation and incubated for 48 hours at 37° C by means of the plate incorporation method. In the 2nd trial, the bacterial strains were preincubated with the test material for 20 minutes prior to incorporation into the agar. Each treatment was incubated in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 8/19/09)

** 53082-0198; 243601; "V79/HPRT-Test *In Vitro* for the Detection of Induced Forward Mutations"; (B. Herbold; Bayer HealthCare AG, PH-GDD Toxicology, 42096 Wuppertal, Germany; Study No. T 5076147; 8/30/06); Chinese hamster V79 cells were exposed to AE 1170437 technical (batch no. EFIM000511; purity: 90.32%) for 5 hours at 37° C at concentrations ranging from 15 to 150 µg/ml w/o activation and from 10 to 320 ug/ml with activation. Two trials were performed with duplicate cultures for each treatment level. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the mutation frequency in either of the trials. **No adverse effect indicated.** The positive controls were functional. **Study acceptable.** (Moore, 8/20/09)

CHROMOSOME EFFECTS

**** 53082-0200; 243603**; "*In Vitro* Chromosome Aberration Test with Chinese Hamster V79 Cells"; (M. Nern; Bayer HealthCare AG, PH-GDD Toxicology, 42096 Wuppertal, Germany; Study No. T 4076146; 9/4/06); Chinese hamster V79 were exposed to concentrations of AE 1170437 technical (batch no. EFIM000511; purity: 90.32%) ranging from 15 to 120 ug/ml w/o activation and from 50 to 240 ug/ml with activation for 4 hours at 37° C. Cells were harvested at 18 or 30 hours after the beginning of the treatment. In addition, cells were exposed to the test material for 18 hours at concentrations ranging from 4 to 24 ug/ml w/o activation. One trial was performed. Duplicate cultures were incubated for each treatment level. An Aroclor 1254-induced rat liver S9 fraction was used for activation. An increased incidence of chromosomal exchanges occurred with activation. **Possible adverse effect indicated**. The positive controls were functional. **Study acceptable**. (Moore, 8/24/09)

DNA DAMAGE

** 53082-0204; 243607; "Micronucleus-Test on the Male Mouse"; (B. Herbold; Bayer HealthCare AG, PH-GDD Toxicology, 42096 Wuppertal, Germany; Study No. T 6076148; 8/2/06); Five male Hsd/Win mice/group were dosed twice by intraperitoneal (ip) injection with 0, 10, 20 or 40 mg/kg of AE 1170437 technical (batch no. EFIM000511; purity: 90.32%) with a 24 hour interval between injections (note: an additional group of 5 males were treated with 40 mg/kg twice as a reserve). The animals were euthanized 24 hours after the second injection. The vehicle was an aqueous 0.5% cremophor emulsion. A positive control group of five males also received a single ip injection with 20 mg/kg of cyclophosphamide and was euthanized at 24 hours post-dose. The femoral bone marrow was harvested and evaluated for the presence of micronuclei in both polychromatic and normochromatic erythrocytes. Two thousand polychromatic erythrocytes were evaluated per animal. Treatment-related signs included apathy, roughened fur, spasms and difficulty in breathing. There was no treatment-related increase in the number of micronuclei per 2000 polychromatic erythrocytes. The positive control was functional. **No adverse effect indicated. Study acceptable.** (Moore, 8/28/09)

NEUROTOXICITY

Rat Acute Neurotoxicity Study

53082-0206; 243609; "An Acute Oral Neurotoxicity Screening Study with Technical Grade BCS-AA10717 in Wistar Rats"; (R.G. Gilmore, H.E. Hoss; Bayer CropScience LP, Toxicology, Stilwell, KS; Report No. 201782; 4/29/08); Twelve Wistar rats/sex/group were dosed orally by gavage with 0, 100, 500 or 2000 mg/kg of Technical Grade BCS-AA10717 (lot no. EFIM000511; purity: 93.14% (analyzed 11/06)). Due to the deaths of 3 of 6 dosed females in the 2000 mg/kg group within 24 hours post-dose, the 2nd cohort of 6 females were not treated. A follow-up study was performed in which 12 females/group were dosed with 0, 25 or 50 mg/kg of the test material. Functional observational battery and motor activity evaluations were performed prior to treatment, at 50 minutes post-dose (time to peak effect) and on days 7 and 14. The mean body weight gain of the 2000 mg/kg males and the 500 mg/kg females was less than that of the control group during the 1st week of the study. Clinical signs of tremors and increased and/or decreased activity were noted for the females in the 500 mg and 2000 mg/kg groups. The males in the 500 and 2000 mg/kg groups demonstrated increased urine staining. Motor and locomotor activities of the 2000 mg/kg males and the 500 mg/kg females were less than the control values at 50 minutes post-dose. Although the report's authors stated the 100 mg/kg females had reduced activities as well, this effect was not apparent. In the micropathological evaluation, degeneration of nerve fibers was noted in the gasserian ganglion and sciatic and tibial nerves of the 2000 mg/kg males. **Possible adverse effect:** tremors and neuronal degeneration. **Rat Acute Neurotoxicity NOEL:** (M) 500 mg/kg (based upon reduced motor activity and lesions in the neuronal tissue of the 2000 mg/kg; males), (F) 100 mg/kg (based upon clinical signs in the 500 mg/kg group females); **Study acceptable.** (Moore, 9/2/09)

Rat Subchronic Neurotoxicity Study

**** 53082-0205; 243608**; "A Subchronic Neurotoxicity Screening Study with Technical Grade BCS-AA10717 in Wistar Rats"; (R.G. Gilmore, H.E. Hoss; Bayer CropScience LP, Toxicology, Stilwell, KS; Report No. 201749; 2/21/08); Twelve Wistar rats/sex/group (unless otherwise noted) received 0, 200, 4000, 8000 (females only) or 10000 (males only) ppm of Technical Grade BCS-AA10717 (lot no. EFIM000511; purity: 93.14% (analyzed 11/06)) in the diet for 13 weeks ((M) 0, 12.2, 243.6, 585.7 mg/kg/day, (F) 0, 15.1, 306.9, 580.9 mg/kg/day). No deaths occurred during the study. The mean body weights of both sexes in the high dose groups were lower than those of the control group over the course of the study (NS, $p<0.05$). The mean food consumption of both sexes in the high dose group was less than the control group during the study (NS, $p<0.05$). In the Functional Observational Battery, one or two animals of both sexes in the high-dose groups demonstrated clinical signs of tremors, repetitive chewing movements and/or perianal staining. These observations were sporadic over the course of the study. No treatment-related effects were noted in the ophthmalogical examination. The motor and locomotor activities of the high dose females were less than the control values throughout the study (NS, $p<0.05$). In the necropsy examination, no treatment-related effect was noted upon the brain weights. In the micropathology, no treatment-related lesions in the nervous tissues were evident. **Possible adverse effect:** tremors**. Rat Subchronic Neurotoxicity NOEL:** (M/F) 4000 ppm ((M) 243.6 mg/kg/day, (F) 306.9 mg/kg/day) (based upon incidence of clinical signs in the FOB and the lower motor and locomotor activities of the high dose animals); **Study acceptable.** (Moore, 8/31/09)

Rat Developmental Neurotoxicity

** 53082-0182; 243585; "A Developmental Neurotoxicity Study with Technical Grade BCS-AA10717 in Wistar Rats"; (L.P. Sheets, R.G. Gilmore, H.E. Hoss; Bayer CropScience LP, Toxicology, Stilwell, KS; Report No. 201877; 7/1/08); Thirty mated female Wistar rats/group received 0, 150, 1000 or 7000 ppm of Technical Grade BCS-AA10717 (previously referred to as AE 1170437) (batch no. EFIM000511; purity: 93.14%) in the diet from day 6 of gestation through day 21 of lactation. On lactation day 4, the 7000 ppm dietary mixture was lowered to 4000 ppm. Intake of the test material was reported to 0, 13.0, 83.8, and 568/432 mg/kg/day, respectively. (note: the concentration of the test material in the dietary preparations was adjusted to the expected food consumption during the lactation period in order to maintain a reasonably constant level of test material consumption during this period). Offspring from 23 litters in the control and

150 ppm groups, from 21 litters in the 1000 ppm group and from 19 litters in the 7000/4000 ppm group were assessed neurologically up to 75 days post-natal in the functional observational battery (FOB), measurement of motor activity, auditory startle response, passive avoidance learning and memory and water maze learning and memory assessments. The neuropathologic examination and morphometric analysis of selected neurological tissues from the pups were performed. The mean body weight of the 7000/4000 ppm dams was less than the control values through lactation day 4 ($p<0.01$). Once the treatment level was adjusted to 4000 ppm, the effect on the body weight was attenuated. The mean food consumption was not affected by the treatment. Clinical signs included coarse tremors during the gestation period for the dams in the 7000/4000 ppm. Dilated pupils were noted in 7 dams in this group during the gestation period and in 4 dams during the lactation period. Effects were not apparent after the dose level was reduced on lactation day 4. In the FOB, on gestation days 13 and 20, dilated pupils were noted for 7000/4000 ppm dams. On day 20 alone, unresponsive pupils were noted for 2 animals, tremors in one animal and repetitive chewing movements for 3 of them in this group. No effects were noted on lactation days 11 and 21. This was likely due to the reduction in the dose level on lactation day. In the ophthalmological examination, no treatment-related effects were noted. For the pups, the mean body weight of those in the 7000/4000 ppm group was less than the control value through day 11 of lactation ($p<0.01$ or 0.05). There was no treatment-related effect on the live birth, viability or lactation indices. No treatment-related effect was noted for the developmental landmarks. No treatment-related effects were noted for the pups in the FOB assessments. In the motor and locomotor activity assessments of the pups, the 7000/4000 ppm males demonstrated a lower level of activity than the control group on post-natal day 21 ($p<0.05$). However, this effect was not evident at any other time points during the study. In the auditory startle habituation, passive avoidance and water maze assessments, no treatment-related effect was evident. In the necropsy examination, no treatment-related gross lesions were evident in the neurological tissues and the brain weights were not affected at either post natal day 21 or 75. No microscopic lesions were identified as treatment-related in the histopathological evaluation. In the morphometric analysis of the brain, the anterior to posterior cerebrum length of the 7000/4000 ppm females was less than that of the control group on post natal day 75 ($p<0.05$). However, this decrement in length was not deemed to be treatment-related because all of the other measured parameters were not affected by the treatment and the observed value was within the historical control range. **No adverse effect indicated. Maternal NOEL:** 1000 ppm (83.3 mg/kg/day (based upon lower mean body weights and clinical signs demonstrated by the 7000/4000 ppm dams); **Developmental NOEL:** 1000 ppm (83.3 mg/kg/day (based upon the lower mean body weights of the offspring in the 7000/4000 ppm group); **Developmental Neurotoxicity NOEL:** 7000/4000 ppm (568/432 mg/kg/day) (based upon the lack of a neurologically-related effect noted in the offspring at the highest dose tested). **Study acceptable.** (Moore, 8/11/09)

METABOLISM STUDIES

53082-0183; 243586; "The Metabolism of [^{14}C] AE 1170437 in Rats"; (M.E. Krolski, T. Nguyen; Bayer CropScience, Environmental Research, Bayer Research Park, Stilwell, KS; Report No. MEDHP016; 6/30/08); Four male Wistar Hanover rats/group were dosed orally by gavage with 11.50 mg/kg of [Indane-3-^{14}C] AE 1170437 (reference no. BECH 1673, specific activity: 29.7 mCi/mMole, radiochemical purity: 99%) or 14.98 mg/kg of [Triazine-2,4-^{14}C] AE 1170437 (reference no. 2005BRP022-0022, 28.8 mCi/mMole, radiochemical purity: 100%) (Experiment A). In Experiment B, 4 and 5 male bile duct-cannulated rats were dosed orally by gavage with 14.00 mg/kg of [Indane-3-^{14}C] AE 1170437 or with 13.35 mg/kg of [Triazine-2,4-^{14}C] AE 1170437, respectively. In Experiment A, urine and feces samples were collected up to 72 hours post-dose. Exhaled carbon dioxide collection was discontinued at 48 hours post-dose due to the lack of radiolabel in the samples. In Experiment B, urine, bile and feces samples were collected up to 48 hours post-dose. Tissues were assayed for the presence of radiolabel at the end of the respective sampling periods. Composite urine, bile and fecal samples were analyzed by HPLC, mass spectroscopy and nuclear magnetic resonance in order to identify the metabolites of the parent compound. In both experiments, the excretion of the radiolabel in the urine ranged from 35 to 49% of the administered dose. The location of the label on the molecule did not appear to affect the excretion percentage. In Experiment A, 62 and 70% of the label was excreted in the feces. In the second experiment, this percentage was reduced to 20 and 10% of the administered

dose, respectively. Recovery in the bile constituted 48 and 38% of the dose. Approximately 90% of the test material was absorbed. Eighty four to 90% of the administered dose was excreted within the first 24 hours post-dose. The radiolabel was not sequestered in any particular tissue or organ. Among the metabolites recovered, oxidation of the methyl group on the benzyl moiety to the carboxylic acid was the predominant pathway. In Experiments A and B, this metabolite comprised 63 to 67% and 37 to 39%, respectively, of the administered dose. Further oxidation of the indane ring resulted in the formation of the 3-hydroxyindane acid and the 3-ketoindane acid. Formation of the dihydroxy moiety was also a precursor of the 3-hydroxyindane acid. Gluronic acid conjugates of the hydroxylated moieties were also isolated. Unmetabolized parent compound ranged from 2 to 15% of the administered dose. **Study acceptable.** (Moore, 8/13/09)

53082-0243; 248891; "The Metabolism of [^{14}C] AE 1170437 in Rats (Additional Groups)"; (M.E. Krolski, T. Nguyen; Bayer CropScience, Environmental Research, Bayer Research Park, Stilwell, KS; Report No. MEDHP023; 4/3/09); Two experiments were performed in which Wistar Hanover rats were dosed orally by gavage with either [Indane-3-^{14}C] AE 1170437 (reference no. BECH 1673, specific activity: 29.7 mCi/mMole, radiochemical purity: 99%) or [Triazine-2,4-^{14}C] AE 1170437 (reference no. 2005BRP022-0022, 28.8 mCi/mMole, radiochemical purity: 100%). In the excretion experiment, 4 females/group were dosed with 4.84 mg/kg of the indane-labeled test material or 8.85 mg/kg of the triazine-labeled test material and 4 males/group were dosed with 558.7 mg/kg of the indane-labeled test material and 722.8 mg/kg of the triazine-labeled test material. In the pharmacokinetic study, 3 or 4 animals/sex/group were treated with doses which ranged from 13.28 to 16.91 mg/kg of one or the other of the two test materials. In the excretion experiment, urine and fecal samples were collected up to 72 or 96 hours post-dose. Exhaled carbon dioxide collection from the females was discontinued at 48 hours post-dose due to the lack of radiolabel in the samples. Tissues were assayed for the presence of radiolabel at the end of the respective sampling periods. Composite urine and fecal samples were analyzed by HPLC, mass spectroscopy and nuclear magnetic resonance in order to identify the metabolites of the parent compound. In the pharmacokinetic experiment, blood samples were drawn from a cannula in the jugular vein up to 72 hours post-dose. In the excretion experiment, 44 to 49% and 42 to 49% of the administered radiolabel was recovered in the urine and feces of the low-dose females, respectively. Eighty eight to 89% of administered dose was excreted in the first 24 hours. For the high-dose males, 6 to10% of administered dose was excreted in the urine and 90 to 100% was recovered in the feces. In the first 24 hours, 93 to 105% of the administered dose was excreted. The location of the label on the molecule did not appear to affect the excretion percentage for either the males or the females. The radiolabel was not sequestered in any particular tissue or organ. Among the metabolites recovered, oxidation of the methyl group on the benzyl moiety to the carboxylic acid was the predominant pathway. This metabolite comprised 57 to 59% and 49 to 53% of the administered dose for the low-dose females and the high-dose males, respectively,. Further oxidation of the indane ring resulted in the formation of the 3-hydroxyindane acid and the 3-ketoindane acid. Formation of the dihydroxy moiety was also a precursor of the 3-hydroxyindane acid. Glucuronic acid conjugates of the hydroxylated moieties were also isolated. Unmetabolized parent compound ranged from 36 to 38% of the administered dose for the high-dose males. In the pharmacokinetic study, peak blood levels were achieved at 40 to 60 minutes post-dose. **Study supplemental** (additional information to supplement the guideline metabolism study). (Moore, 9/28/09)

SUBCHRONIC STUDIES

Rat Subchronic Dietary Toxicity Study

** 53082-0176; 243579; "AE 1170437: 90-Day Toxicity Study in the Rat by Dietary Administration"; (A. McElligott; Bayer CropScience BP 153, 06903 Sophia Antipolis Codex, France; Study No. SA 04093; 4/27/05); Ten Wistar rats/sex/group received 0, 200, 5000 or 10000

ppm of AE 1170437 Technical (batch no. NLL 7482-5A; purity: 98.7%) in the diet for 13 weeks ((M) 0, 13.5, 338, 689 mg/kg/day, (F) 0, 16.0, 410, 806 mg/kg/day). A recovery cohort of ten animals/sex/group in the control and 10000 ppm groups were maintained for another 4 weeks without treatment. Two males in the control group died during the study. One was found dead on day 16 and the other was euthanized for humane reasons on day 85. One female in the 10000 ppm group was euthanized for humane reasons on day 20. The mean body weight gain of both sexes in the 10000 ppm group was less than that of the control group over the course of the study ($p<0.05$). The mean body weights of both sexes in the 10000 ppm were still lower than those of the control group at the conclusion of the recovery period ($p<0.05$). The mean food consumption of the females in the 10000 ppm group was less than the control group animals at various times during the treatment period ($p<0.05$). No treatment-related effect was evident in the motor activity, reflex or grip strength assessments. The ophthalmology, hematology or urinalysis parameters were not affected by the treatment. In the clinical chemistry evaluation, the thyroid stimulating hormone levels of the 5000 and 10000 ppm males were elevated in comparison to the control group after 3 weeks of treatment ($p<0.05$). After 13 weeks of treatment, the differences in the TSH levels between these groups and the control animals were not statistically significant. No treatment-related effects on the T3 and T4 levels in the blood were evident at either 3 or 13 weeks of treatment. The mean relative liver weights of both sexes in the 5000 and 10000 ppm groups were greater than the control values at the end of the treatment period ($p<0.01$ or 0.05). The mean relative kidney weights of both sexes in the 10000 ppm group were greater than control values at the end of the treatment period ($p<0.01$ or 0.01). The mean relative kidney weight of the 10000 ppm males was still greater than that of the control at end of the recovery period ($p<0.05$). In the histopathology evaluation, an increase in the incidence of interstitial mononuclear cell infiltrate, focal and/or multifocal, was noted in the kidneys of the 5000 and 10000 ppm males (0: 1/8 vs. 5000: 7/10, 10000: 7/10). Diffuse follicular cell hypertrophy was evident in the thyroid glands of the 5000 and 10000 ppm males (0: 0/8 vs. 5000: 5/10, 1000: 9/10). Unilateral or bilateral pelvic dilatation of the kidney was noted for the 5000 and 10000 ppm females (0: 0/10 vs. 5000: 3/10, 10000: 6/10). **No adverse effect indicated. Rat Subchronic Dietary NOEL:** (M/F) 200 ppm ((M) 13.5 mg/kg/day, (F) 16.0 mg/kg/day) (based upon lesions in the kidneys of both sexes in the 5000 ppm group and follicular cell hypertrophy in the thyroid gland of the 5000 ppm males). **Study acceptable.** (Moore, 7/23/09)

Rat 4-Week Repeated Dosing Dermal Toxicity Study

** 53082-0179; 243582; "AE 1170437: Subacute Toxicity Study in Wistar Rats (4 Weeks Dermal Administration)"; (L. Schladt; Bayer HealthCare AG, PH-GDD Toxicology, 42096 Wuppertal, Germany; Study No. T3076802; 8/29/06); The skin of 10 Wistar rats/sex/group was exposed to 0, 40, 200 or 1000 mg/kg/day of AE 1170437 Technical (batch no. EFIM000511; purity: 90.32%) for 6 hours/day, 5 days per week for the first 3 weeks and then daily for 7 (males) or 8 (females) days prior to the termination of the study. The test material was placed on a moistened gauze and then placed on the skin. No deaths resulted from the treatment. No treatment-related effect on mean body weights or food consumption was evident. No treatment-related effect was noted in the hematology and clinical chemistry evaluations, ophthalmology or necropsy and histopathology examinations. **No adverse effect indicated. Rat Repeated Dosing Dermal Toxicity NOEL:** (M/F) 1000 mg/kg/day; **Study acceptable**. (Moore, 10/26/09)

Mouse Subchronic Dietary Toxicity Study

53082-0177; 243580; "AE 1170437: 90-Day Toxicity Study in the Mouse by Dietary Administration"; (A. McElligott; Bayer CropScience BP 153, 06903 Sophia Antipolis Codex, France; Study No. SA04094; 2/28/05); Ten C57BL/6J mice/sex/group received 0, 100, 500 or 1200 ppm of AE 1170437 Technical (batch no. BCTM1130-2; purity: 96.5%) in the diet for 13 weeks ((M) 0, 19.0, 91, 218 mg/kg/day, (F) 0, 22.7, 118, 256 mg/kg/day). One female in the 1200 ppm group was euthanized for humane reasons on day 10. One male in the control group was found dead on day 85. The mean body weights of both sexes in the 1200 ppm group were less than those of the control group through out the study ($p<0.01$). The mean food consumption of these animals was also less than that of the control group ($p<0.01$ or 0.05). In the clinical chemistry evaluation, the total protein or albumin concentrations in the serum of both sexes in the 1200 ppm group were less than those of the control group ($p<0.01$). The mean absolute liver and

kidney weights of the 1200 ppm males were less than the control values (p<0.01). The mean relative liver weight of the 1200 ppm females was greater than that of the control group (p<0.01). The mean absolute kidney weight of the 1200 ppm females was less than that of the control group (p<0.05). The mean absolute and relative spleen weights of the 1200 ppm females were less than the control group values (p<0.01 or 0.05). No treatment-related lesions were evident in the histopathological examination. **No adverse effect indicated. Mouse Subchronic Dietary NOEL:** (M/F) 500 ppm ((M) 91 mg/kg/day, (F) 118 mg/kg/day) (based upon the lower mean body weights and food consumption of both sexes in the 1200 ppm treatment group). **Study supplemental** (study protocol did not include certain parameters required for a rodent subchronic dietary toxicity study, i.e., ophthalmology, hematology, a full clinical chemistry screen). (Moore, 7/27/09)

Dog Subchronic Oral Toxicity Study

**** 53082-0178; 243581**; "A 90-Day Toxicity Study in the Beagle Dog with Technical Grade BCS-AA10717 Administered by Oral Gavage"; (D.A. Eigenberg; Bayer CropScience LP, Toxicology, Stilwell, KS; Report No. 201630; 6/26/08); Four beagle dogs/sex/group were dosed orally by gavage with 0 (vehicle: aqueous 0.5% methylcellulose), 7.5, 15.0 or 30.0 mg/kg/day of Technical Grade BCS-AA10717 (lot no. EFIM000511; purity: 94.5% (analyzed 12/05)) for 13 weeks. Three dogs in the 30 mg/kg group were euthanized *in extremis* on study days 15, 22 and 35 due to seizures. The remaining animals in this group were removed from the study on day 35 for humane reasons. Among the clinical signs which were noted, the 15.0 and 30 mg/kg animals demonstrated an increase in salivation and exhibited tremors. Three of the eight 30 mg/kg animals suffered seizures and two of them had ataxia. The mean body weights and food consumption were not affected by the treatment. No treatment-related effects were noted in the clinical chemistry and hematology evaluations, the urinalysis and ophthalmological examination. The mean absolute and relative liver weights of the 30 mg/kg males were greater than the control group (p<0.05, NS) even though all of these animals were removed from the study after 5 weeks of treatment. In the histopathological evaluation, axonal degeneration was noted in the spinal cord and sciatic nerves of both sexes in the 15.0 and 30.0 mg/kg groups and in the brain of the females in the 15.0 and 30.0 mg/kg groups. Axonal swelling was evident in the brain and/or spinal cord of both sexes in the 7.5 mg/kg group. **Possible adverse effect:** seizures and lesions in the nerve tissue; **Dog Subchronic Oral Toxicity NOEL:** (M/F) < 7.5 mg/kg (based upon the incidence of axonal swelling in the brain and/or spinal cord of both sexes in the 7.5 mg/kg group). **Study acceptable.** (Moore, 7/28/09)

Immunotoxicity, Rat

** 53082-0184; 243587; "Subacute Oral Immunotoxicity Study in Wistar Rats (4 Weeks Administration in Diet)"; (E. Reibmuller, H.W. Vohr; Bayer HealthCare AG, BSP-GDD-GED General Toxicology, 42096 Wuppertal, Germany; Study No. T 7078589; 5/29/08); Eight Wistar rats/sex/group (except where noted) received 0, 300, 3000, 6000 (females only) or 10000 (males only) ppm in the diet for at least 29 days. The dietary preparation for the 10000 ppm males was reduced on day 16 due to the severity of the treatment-related effects. Test material uptake was 0, 27.7, 258.8, and 528.0 mg/kg/day for the males and 0, 31.0, 334.2 and 737.9 mg/kg/day for the females. Five days before necropsy, the tail vein of the study animals was injected with sheep red blood cells (SRBC)/ml. SRBC specific IgM plaques were determined for each animal in duplicate by incubating a spleen cell suspension preparation with guinea pig complement. The numbers of Plaque-Forming Cells (PFC) per 10^6 spleen cells was determined. One male in the 10000 ppm group was euthanized *in extremis* on study 12. The mean body weights of the 10000 ppm males and the 6000 ppm females were less than those of the control group throughout the study (p<0.01 or 0.05). The mean food consumption of the 10000 ppm males was significantly less than that of the control males over the course of the study. Likewise, water consumption for this group was also less than that of the control group. The mean absolute thymus and spleen weights of the 10000 ppm males were less than the control values (p<0.01). However, the relative weights for these organs were not affected by the treatment. Although the concentration of plaque-forming cells in the spleens of the treated animals were greater in the control, no treatment-related response was evident. **No adverse effect indicated. Study acceptable.** (Moore, 8/17/09)

MECHANISTIC STUDY

53082-0185; 243588; "A Special Study to Evaluate Sexual Maturation in Female Wistar Rats"; (A.D. Milius, H. Hoss; Bayer CropScience LP, Toxicology, Stilwell, KS; Report No. 201880; 6/23/08); Fifteen 21-day old female pups/group were dosed orally by gavage with 0 (vehicle: aqueous 1% methylcellulose), 18.0, 36.5, 72.9 or 145.8 mg/kg/day of BCS-AA10365 (major metabolite, 6-(1-fluoroethyl)-1,3,5-triazine-2,4-diamine) (lot no. KATH4923-14-1, purity: 98.7%) from day 22 to day 41 post-natal. A positive control group of fifteen 21-day old pups was treated with 135 mg/kg/day of 2-chloro-4,6-diamino-1,3,5-triazine (DACT) for the same time interval. This treatment level was reduced to 67.5 mg/kg/day after one week of treatment due to the deaths of two of the pups. No deaths resulted from the treatment with BCS-AA10365. Clinical signs included an increased incidence of urine stain and salivation in the 145.8 mg/kg group. The mean body weight gain of the 72.9 and 145.8 mg/kg groups were lower than the control group over the course of the treatment period ($p<0.05$). The time to vaginal patency was delayed for the 72.9 and 145.8 mg/kg treatment groups. The mean body weights of the treated animals were greater than the control group at the time patency was achieved. The positive control was functional. **Study supplemental.** (Moore, 8/17/09)

STUDIES ON METABOLITES

Gene Mutation

** 53082-0195; 243598; "*Salmonella*/Microsome Test: Plate Incorporation and Preincubation Method"; (B. Herbold; Bayer HealthCare AG, PH-GDD Toxicology, 42096 Wuppertal, Germany; Study No. T 2077198; 6/27/07); *S. typhimurium* TA98, TA100, TA102, TA1535 and TA1537 strains were incubated with 6-(1-Fluorophenyl)-1,3,5-Triazin-2,4-Diamine (metabolite) (BCS-AA10365) (batch no. KATH4923-14-1; purity: 98.7%) at levels ranging from 16 to 5000 µg/plate (both trials) under conditions of (-/+) activation and incubated for 48 hours at 37° C by means of the plate incorporation method. In the 2nd trial, the bacterial strains were preincubated with the test material for 20 minutes prior to incorporation into the agar. Each treatment was incubated in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 8/18/09)

** 53082-0196; 243599; "*Salmonella*/Microsome Test: Plate Incorporation and Preincubation Method"; (B. Herbold; Bayer HealthCare AG, BSP-GDD-GED-GTOX Genetic Toxicology, 42096 Wuppertal, Germany; Study No. T 5077993; 12/12/07); *S. typhimurium* TA98, TA100, TA102, TA1535 and TA1537 strains were incubated with AE 1170437-carboxylic acid (batch no. RDL 108-14-8; purity: 96.5%) at levels ranging from 16 to 5000 µg/plate (both trials) under conditions of (-/+) activation and incubated for 48 hours at 37° C by means of the plate incorporation method. In the 2nd trial, the bacterial strains were preincubated with the test material for 20 minutes prior to incorporation into the agar. Each treatment was incubated in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 8/19/09)

** 53082-0199; 243602; "V79/HPRT-Test *In Vitro* for the Detection of Induced Forward Mutations"; (G. Entian; Bayer HealthCare AG, PH-GDD Toxicology, 42096 Wuppertal, Germany; Study No. T 6077200; 8/14/07); Chinese hamster V79 cells were exposed to 6-(1-Fluorophenyl)-1,3,5-Triazin-2,4-Diamine (metabolite) (BCS-AA10365) (batch no. KATH4923-14-1; purity: 98.7%) for 5 hours at 37° C at concentrations ranging from 50 to 1600 µg/ml with and w/o activation. Two trials were performed with duplicate cultures for each treatment level. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the mutation frequency in either of the trials. **No adverse effect indicated.** The positive controls were functional. **Study acceptable.** (Moore, 8/20/09)

** 53082-0201; 243604; "V79/HPRT-Test *In Vitro* for the Detection of Induced Forward Mutations"; (G. Entian; Bayer HealthCare AG, BSP-GDD-GED-GTOX Genetic Toxicology, 42096 Wuppertal, Germany; Study No. T 7077995; 4/17/08); Chinese hamster V79 cells were exposed to AE 1170437-carboxylic acid (batch no. RDL 108-14-8; purity: 96.5%) for 5 hours at 37° C at

concentrations ranging from 400 to 2400 µg/ml with and w/o activation. Three trials were performed w/o activation and two trials were performed under conditions of activation with duplicate cultures for each treatment level. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the mutation frequency in either of the trials. **No adverse effect indicated.** The positive controls were functional. **Study acceptable.** (Moore, 8/25/09)

Chromosome Effects

** 53082-0202; 243605; "*In Vitro* Chromosome Aberration Test with Chinese Hamster V79 Cells'; (M. Thum; Bayer HealthCare AG, PH-GDD Toxicology, 42096 Wuppertal, Germany; Study No. T 3077199; 6/28/07); Chinese hamster V79 were exposed to concentrations of 6-(1-Fluorophenyl)-1,3,5-Triazin-2,4-Diamine (metabolite) (BCS-AA10365) (batch no. KATH4923-14-1; purity: 98.7%) ranging from 325 to 1300 ug/ml with and w/o activation for 4 hours at 37° C. Cells were harvested at 18 or 30 hours after the beginning of the treatment. In addition, cells were exposed to the test material for 18 hours at concentrations ranging from 150 to1300 ug/ml w/o activation. One trial was performed. Duplicate cultures were incubated for each treatment level. An Aroclor 1254-induced rat liver S9 fraction was used for activation. No increase in chromosomal aberrations was noted with or w/o activation. **No adverse effect indicated**. The positive controls were functional. **Study acceptable**. (Moore, 8/26/09)

**** 53082-0203; 243606**; "*In Vitro* Chromosome Aberration Test with Chinese Hamster V79 Cells "; (M. D'Acquisto; Bayer HealthCare AG, BSP-GDD-GED-GTOX Genetic Toxicology, 42096 Wuppertal, Germany; Study No. T 6077994; 12/13/07); Chinese hamster V79 were exposed to concentrations of AE 1170437-carboxylic acid (batch no. RDL 108-14-8; purity: 96.5%) ranging from 400 to 1800 ug/ml w/o activation and from 500 to 2400 ug/ml with activation for 4 hours at 37° C. Cells were harvested at 18 or 30 hours after the beginning of the treatment. In addition, cells were exposed to the test material for 18 hours at concentrations ranging from 175 to 1100 ug/ml w/o activation. One trial was performed. Duplicate cultures were incubated for each treatment level. An Aroclor 1254-induced rat liver S9 fraction was used for activation. An increased incidence of chromosomal aberrations occurred w/o activation. **Possible adverse effect indicated**. The positive controls were functional. **Study acceptable**. (Moore, 8/27/09)