CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Fluopicolide

Chemical Code #5949 , **Tolerance** # 53014
SB 950 # NA

May 2, 2007

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect evident
Chronic toxicity, dog:	No data gap, no adverse effect evident
Oncogenicity, rat:	No data gap, no adverse effect evident
Oncogenicity, mouse:	No data gap, possible adverse effect
Reproduction, rat:	No data gap, no adverse effect evident
Teratology, rat:	No data gap, no adverse effect evident
Teratology, rabbit:	No data gap, no adverse effect evident
Gene mutation:	No data gap, possible adverse effect evident
Chromosome effects:	No data gap, possible adverse effect evident
DNA damage:	No data gap, no adverse effect evident
Neurotoxicity:	No studies submitted nor required at this time

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Toxicology one-liners are attached.

All record numbers through 232106 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T070502
Revised by T. Moore, 5/2/07

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

COMBINED, RAT

** 53014-0148; 230028; "AE C638206: Combined Carcinogenicity and Toxicity Study by Dietary Administration to CD Rats for 104 Weeks"; (S. Cooper; Huntingdon Life Sciences Ltd., Alconbury, Huntingdon, Cambridgeshire, PE28 4HS, England; Project ID. AES 024/032124; 11/18/03); Sixty Crl:CE (SD)IGS BR rats/sex/group received 0, 50, 200, 750 or 2500 ppm of AE C638206 Technical (batch no. OP2050046, purity: 95.9%) in the diet for 2 years (carcinogeneity phase) ((M) 0, 2.10, 8.35, 31.5, 109.4 mg/kg/day, (F) 0, 2.81, 10.8, 41.0, 142.2 mg/kg/day). An additional 30 animals/sex/group received the treatment for 52 weeks. Of these animals, 20 per sex per group were euthanized at that time (toxicity phase) and the remaining 10 animals/sex/group were maintained for a 13-week recovery period (recovery cohort). The survival of the treated groups was not affected by the treatment. The mean body weights and food consumption of both sexes in the 2500 ppm group were less than the control values over the course of the study. In the hematology evaluation, the mean red blood cell count, hematocrit and hemoglobin concentrations of both sexes in the 2500 ppm group were less than the control values at various times during the study ($p<0.05$ or 0.01). However, the effect was not physiologically significant. No treatment-related effects were apparent in the clinical chemistry evaluation, urinalysis or ophthalmology. In the necropsy examination, the mean absolute and relative liver weights of the 2500 ppm males after 52 and 104 weeks of treatment were greater than those of the controls ($p<0.05$ or 0.01). The mean relative liver weights of males in the 750 ppm group and females in the 2500 ppm group were greater than the control values after 52 weeks of treatment ($p<0.05$ or 0.01). The mean relative kidney weights of the 750 ppm males and both sexes in the 2500 ppm group were greater than the control values after 52 weeks of treatment ($p<0.05$ or 0.01). The mean absolute and relative kidney weights of the 750 and 2500 ppm males were greater than those of the controls after 104 weeks of treatment ($p<0.05$ or 0.01). In the histopathology examination, centrilobular hepatocytic hypertrophy was noted in the livers of the males in the 750 and 2500 ppm groups after both 52 and 104 weeks of treatment (52 weeks, 0: 0/20 vs. 750: 14/20, 2500: 19/20; 104 weeks, 0: 0/60 vs. 750: 9/60, 2500: 18/60). The incidences of cystic degeneration, clear cell foci and eosinophilic foci were increased in the livers of the 2500 ppm males after 104 weeks of treatment as well. There were increased incidences of cortical tubular basophilia, cortical tubules with hyaline droplets, granular casts in the medulla and hyaline tubular casts in the kidneys of the 2500 ppm males after 52 weeks of treatment. After 104 weeks of treatment, the kidneys of the males in the 2500 ppm group exhibited an increased incidence of tubular casts, cortical tubular dilatation, cortical tubules with hyaline droplets, cortical cysts and mineralization of the papilla. The prostate gland of the males in the 2500 ppm group had an increased incidence of acinar cell atrophy after 104 weeks of treatment. The thyroid gland of these males also demonstrated an increased incidence of cystic follicular cell hyperplasia after 104 weeks of treatment. For the females in the 2500 ppm group, there was an increased incidence of eosinophilic foci in the livers after 104 weeks of treatment. The kidneys of these females had an increased incidence of hyperplasia of the papillary epithelium after 52 weeks of treatment. Any of the lesions apparent after 52 weeks of treatment had been resolved by the end of the 13-week recovery period. **No adverse effect indicated. Rat Chronic Dietary NOEL:** (M) 200 ppm (8.35 mg/kg/day) (based upon the incidence of hepatocellular hypertrophy noted for the males in the 750 ppm group), (F) 750 ppm (41.0 mg/kg/day) (based upon the lower mean body weight of the females in the 2500 ppm group); **Oncogenic effects:** not indicated. **Study acceptable.** (Moore, 2/22/07)

CHRONIC TOXICITY, RAT

See Combined, Rat above

CHRONIC TOXICITY, DOG

** 53014-0146; 230026; "AE C638206: 52-Week Toxicity Study by Oral Route (Gavage) in Beagle Dogs"; (G. Chevalier; CIT (Centre International de Toxicologie) BP 563, 27005 Evreux Cedex, France; Study No. 20961 TCC; 11/14/02); Five beagle dogs/sex/group were dosed orally by

gavage with 0, 70, 300 or 1000 mg/kg/day of AE C638206 Technical (batch no. OP2050046; purity: 95.9%) for 52 weeks. One female in the 300 mg/kg group died on day 240, possibly due to aspiration of regurgitated stomach contents. The males in the 1000 mg/kg group did not demonstrate any body weight gain over the course of the study. Both sexes in the 1000 mg/kg group gave evidence of erratic food consumption over the course of the study. The hematology, urinalysis, and ophthalmological examination not reveal any treatment-related effects. In the clinical chemistry evaluation, the 1000 mg/kg females demonstrated a greater serum cholesterol level than that of the control over the course of the study (NS or $p<0.05$). No dose-related effect on the organ weights was apparent. No treatment-related lesions were noted in the histopathological evaluation. **No adverse effect was evident. Dog Chronic Oral Toxicity NOEL:** (M/F) 300 mg/kg/day (based upon the absence of body weight gain for the males and the increased serum cholesterol levels for the females of the 1000 mg/kg group). **Study acceptable.** (Moore, 2/14/07)

ONCOGENICITY, RAT

See Combined, Rat above.

ONCOGENICITY, MOUSE

**** 53014-0147; 230027**; "AE C638206: Carcinogenicity Study by Oral Route (Dietary Admixture) in C57BL/6 Mice"; (G. Chevalier; CIT (Centre International de Toxicologie) BP 563, 27005 Evreux Cedex, France; Study No. 21557 TCS; 11/20/03); Fifty C57BL/6 N mice/sex/group received 0, 50, 400 or 3200 ppm of AE C638206 Technical (batch no. OP2050046, purity: 95.9%) in the diet for 18 months ((M) 0, 7.9, 64.5, 551.0 mg/kg/day, (F) 0, 11.5, 91.9, 772.3 mg/kg/day). There was no apparent treatment-related effect on the survival of the animals. The mean body weights of both sexes in the 3200 ppm group were less than the control values throughout the study ($p<0.01$). The mean body weights of these high dose animals were only 80 to 85% of the control values during the latter part of the study. The mean food consumption of both sexes in the 3200 ppm group was less than that of the controls over the course of the study ($p<0.05$ or 0.01). The serum alkaline phosphatase, ASAT and ALAT activities of the 3200 ppm females were greater than the control values after 52 weeks of treatment ($p<0.01$ or NS). The mean absolute and relative liver weights of both sexes in the 3200 ppm group and the males in the 400 ppm group were greater than those of the controls after 52 and 78 weeks of treatment ($p<0.01$). In the microscopic examination, centrilobular hepatocytic hypertrophy was noted in the livers of both sexes in both the 400 and 3200 ppm treatment groups after 52 and 78 weeks of treatment (52 weeks, (M) 0: 0/10 vs. 400: 5/10, 3200: 10/10, (F) 0: 0/10 vs. 400: 6/10, 3200: 9/10, 78 weeks, (M) 0: 0/50 vs. 400: 20/50, 3200: 49/50, (F) 0: 0/50 vs. 400: 41/50, 3200: 46/50). An increased incidence of altered cell foci was noted in the livers of both sexes in the 3200 ppm group after 78 weeks of study ((M) 0: 1/50 vs. 3200: 18/50, (F) 0: 1/50 vs. 3200: 25/50). An increased incidence of hepatocellular adenoma was evident for the males in the 3200 ppm group after 78 weeks of treatment and for the females after both 52 and 78 weeks of treatment ((M) 0: 5/50 vs. 3200: 11/50 ($p<0.05$), (F) 52 weeks, 0: 0/10 vs. 3200: 3/10, 78 weeks, 0: 1/50 vs. 3200: 16/50 ($p<0.001$). **Possible adverse effect:** increased incidence of hepatic tumors; **Mouse Chronic Dietary NOEL:** (M/F) 50 ppm ((M) 7.9 mg/kg/day, (F) 11.5 mg/kg/day) (based upon the centrilobular hepatocytic hypertrophy noted in the livers of the both sexes in the 400 ppm treatment group); **Possible oncogenicity evident.** (Moore, 2/15/07)

REPRODUCTION, RAT

** 53014-0143, -0144; 2230023, 230024; "AE C638206: Study of Reproductive Performance in CD Rats Treated Continuously Through Two Successive Generations by Dietary Administration"; (M.A.B. Blee; Huntingdon Life Sciences Ltd., Alconbury, Huntingdon, Cambridgeshire, PE28 4HS, England; Report No. 023443; 3/27/03, addendum, 12/16/04); In the F0 generation, 28 CD (Sprague-Dawley origin) rats/sex/group were treated in the diet with 0, 100, 500, or 2000 ppm of AE C638206 Technical (batch no. OP2050046, purity: 95.9%). Twenty-four rats/sex/group received the same treatment in the F1 generation. The treatment periods for the F0 generation included 10 weeks prior to mating, mating, 3 weeks of gestation and 3 weeks of lactation. At that time, F1 animals were selected as parents and treated for 10 weeks, followed by mating and 3 weeks each for gestation and lactation of the F2 generation. There were no apparent treatment-

related deaths among the parents. The mean body weights of the parental rats of both sexes in the 2000 ppm group of both generations were less than the control values ($p<0.05$ or NS). The mean absolute and relative liver of both sexes in the 2000 ppm group of both generation were greater than those values of the control group ($p<0.01$). The absolute and relative kidney weights of the adult males and the relative kidney weights of the females in the 2000 ppm group of both generations were greater than those values of the control group ($p<0.05$ or 0.01). The absolute and relative thyroid weights of the females of the 500 and 2000 ppm group in the F0 generation and the relative thyroid weights of the 2000 ppm F0 males and both sexes of the 2000 ppm group of the F1 generation were greater than the control values ($p<0.05$ or 0.01). Although the relative weights of the prostate, seminal vesicles, epididymides and testes of the 2000 ppm males in the F0 generation were greater than those of the controls ($p<0.05$), the effect was not evident in the F1 generation. No treatment-related lesions were evident in the reproductive tissues and organs of either generation. In the liver, centrilobular hepatocytic hypertrophy was noted for both sexes in the 2000 ppm group and the males of the 500 ppm group of both generations ($p<0.01$). In the kidney, an increased incidence of cortical tubular basophilia was noted for both sexes in the 2000 ppm group of both generations ($p<0.01$). For the males of the 2000 ppm group of both generations, increased incidences of hyaline droplets in the cortical tubules, granular casts in the medulla, interstitial inflammation, cortical scarring and hyaline tubular casts were noted in the kidney as well ($p<0.05$ or 0.01). For the females in the 2000 ppm group, an increased incidence of cortical tubular dilatation was evident in both generations ($p<0.01$). There was no apparent treatment-related effect upon the number of sperm and their morphology or motility for either generation. No treatment-related effect upon time to vaginal opening or preputial separation was evident for the F1 generation. There was no treatment-related effect upon any of the reproductive parameters. In the developmental phase of the study, the mean body weight gain of the 2000 ppm offspring in both generations was less than that of the control from day 14 through day 21 postnatal. **No adverse effect indicated. Parental NOEL: (M)** 100 ppm (5.2 to 14.1 mg/kg/day) (based on centrilobular hypertrophy in the livers of the 500 ppm males of both generations) **(F)** 500 ppm (32.9 to 96.0 mg/kg/day) (based on the lower mean body weights of the females in the 2000 ppm group of both generations and the increased incidence of lesions in the liver and kidneys of the females in the 2000 ppm group of both generations); **Reproductive NOEL:** (M) 103.4 to 206.4 mg/kg/day, (F) 127.3 to 414.9 mg/kg/day) 2000 ppm (based upon the lack of treatment-related effects on reproduction in the 2000 ppm group); **Developmental NOEL:** 500 ppm (M) 25.5 to 70.3 mg/kg/day, (F) 32.9 to 96.0 mg/kg/day)(based upon the lower mean pup weights in the 2000 ppm group of both generations); **Study acceptable**. (Moore, 2/9/07)

53014-0145; 230025; "AE C638206: Preliminary Study of Effects on Reproductive Performance in CD Rats by Dietary Administration"; (M.A.B. Blee; Huntingdon Life Sciences Ltd., Alconbury, Huntingdon, Cambridgeshire, PE28 4HS, England; Report No. 013609; 4/2/02); Eight CD (Sprague-Dawley origin) rats/sex/group received 0, 50, 200, 750 or 2500 ppm of AE C638206 technical (batch no. OP2050046; purity: 95.6%) in the diet for a 15 day premating period, followed by mating and 3-week gestation and lactation periods. Following weaning, 12 F1 animals/sex/group were treated up to 6 weeks of age. Mean intake of the test material during the premating period ranged from 4 to 5, 15 to 18, 59 to 68 and 185 to 208 mg/kg/day for the males and from 4 to 5, 18, 64 to 70 and 175 to 225 mg/kg/day for the females, respectively. The mean test material uptake for the F1 generation between weeks 4 and 6 ranged from 5.5 to 7.2, 20.8 to 27.4, 81.9 to 105, 275 to 362 mg/kg/day for the males and 5.2 to 7.4, 21.0 to 29.0, 79.0 to 115, and 269 to 360 mg/kg/day for the females, respectively. The F0 males in the 750 and 2500 ppm groups had lower mean body weights by end of the premating period**.** In the F1 generation, the pups of both sexes in the 2500 ppm group had lower mean body weights throughout the lactation and post-weaning periods ($p<0.05$ or NS). The viability and lactation indices of the 2500 ppm pups were lower than the control values. The time to vaginal opening was delayed for the 2500 ppm female offspring ($p<0.01$). Based on these study results, treatment levels of 100, 500 and 2000 ppm were chosen for the guideline rat two generation reproduction study. **Study supplemental.** (Moore, 2/7/07)

TERATOLOGY, RAT

** 53014-0141; 230021; "AE C638206: Rat Oral Developmental Toxicity (Teratogenicity) Study (Including Addendum)"; (Th. Hofmann; Aventis Pharma Deutschland GmbH, ProTox, 65795 Hattersheim, Germany; Report No. 2000.0858; 5/10/01, (addendum) 8/9/04); Twenty three mated Sprague-Dawley female rats/group were dosed orally by gavage with 0, 5, 60 or 700 mg/kg/day of AE C638206 technical (batch no. PP241024/2 & PP241067/1, purity: 97.6% (8/23/99), 97.8% (12/1/99)) from gestation day 7 through gestation day 20. No maternal deaths resulted from the treatment. The mean body weight gain of the 700 mg/kg dams was less than that of the control between days 7 and 21. The mean fetal body weight of the 700 mg/kg offspring was less than the control value ($p<0.05$). The mean crown-rump length of the 700 mg/kg fetuses was less than the control value ($p<0.05$). **No adverse effect indicated. Maternal NOEL:** 60 mg/kg/day (based on the lower body weight gain of the 700 mg/kg group); **Developmental NOEL:** 60 mg/kg/day (based on the lower mean body weight and crown-rump length of the fetuses in the 1000 mg/kg group). **Study acceptable.** (Moore, 2/5/07)

53014-0092; 226207; "AE C638206 Code: AE C638206 00 1 C99 0005 Rat Oral Developmental Toxicity (Teratogenicity) Range Finding Study"; Four mated female Sprague-Dawley rats/group were dosed orally by gavage with 500 or 1000 mg/kg/day of AE C638206 (batch no. PP/241024/2 & PP241067/1; purity: 97.6%) from day 7 through day 20 of gestation. The vehicle was aqueous 1% (w/v) methyl cellulose. No deaths resulted from the treatment. One of the dams in the 1000 mg/kg group did not produce a litter. The mean body weight of the 1000 mg/kg group was less than that of the 500 mg/kg group by the end of the gestation period. The mean no. of resorptions/litter was 0 for the 500 mg/kg group and 5.7 for the 1000 ppm group. The number of live fetuses/litter was inversely affected with 13.0 for the 500 mg/kg group and 9.3 for the 1000 mg/kg group. The mean fetal weight and crown-rump length for the 1000 mg/kg offspring were 2.78 g and 32.6 cm as compared to 3.12 g and 34.1 cm for the 500 mg/kg group. There was an apparent treatment-related effect upon both the dams and the development of the fetuses in the 1000 mg/kg group. **Study supplemental** (non-guideline study). (Moore, 12/18/06)

TERATOLOGY, RABBIT

** 53014-0142; 230022; "AE C638206: Rabbit Oral Developmental Toxicity (Teratogenicity) Study (Including Addendum)"; (Th. Hofmann; Aventis Pharma Deutschland GmbH, ProTox, 65795 Hattersheim, Germany; Report No. 2000.0859; 6/20/01, (addendum), 8/9/04); Twenty three mated female Himalayan rabbits/group were dosed orally by gavage with 0, 5, 20 or 60 mg/kg/day of AE C638206 technical (batch no. PP241024/2 & PP241067/1; purity: 97.8%) from day 6 through day 28 of gestation. Three does in the 60 mg/kg group died during the study. Fifteen does in the 60 mg/kg group and 1 doe in the 20 mg/kg group delivered their offspring prematurely. The mean food consumption of the 5 does in the 60 mg/kg group which delivered live fetuses was less than that of the control during the last 6 days of the treatment ($p<0.05$). The mean body weight and crown-rump length of the fetuses in the 60 mg/kg group were less than the respective control values ($p<0.05$). **No adverse effect indicated. Maternal NOEL:** 20 mg/kg/day (based upon the maternal death and premature delivery of the offspring of the does in the 60 mg/kg/day group)
Developmental NOEL: 20 mg/kg/day (based upon the lower mean body weight and the crown-rump length of the fetuses in the 60 mg/kg/day group)**. Study acceptable.** (Moore, 2/6/07)

53014-0093; 226208; "Rabbit Oral Developmental Toxicity (Teratogenicity) Range Finding Study AE C638206 Code: AE C638206 00 1 C99 0005"; (Th. Hofmann; Aventis Pharma Deutschland GmbH ProTox, Hattersheim, 65795 Germany; Project ID. 2000.0467; 11/27/00); Four mated female Himalayan rabbits/group were dosed orally by gavage with 25, 50, 100, 250, 500 or 1000 mg/kg/day of AE C638206 (batch no. PP/241024/2 & PP241067/1; purity: 97.6-97.8%) from day 6 through day 28 of gestation. The vehicle was aqueous 1% methyl cellulose. All of the dams in the 100, 250, 500 and 1000 mg/kg groups died or were euthanized *in extremis* prior to the scheduled sacrifice. One dam in the 50 mg/kg group was euthanized prior to the scheduled sacrifice. The necropsy examination revealed discoloration of the heart, kidneys and liver with petechial bleedings in the stomach. In the one group for which all of the dams survived, 25 mg/kg/day, three of the four dams were pregnant and produced viable litters. No post-

implantation loss was evident and all of the embryos were alive. **Study supplemental** (Non-guideline study). (Moore, 12/18/06)

GENE MUTATION

** 53014-0155; 232094; "AE C638206 00 1B99 0002 (R001737): Reverse Mutation in Four Histidine-Requiring Strains of *Salmonella typhimurium* and One Tryptophan-Requiring Strain of *Escherichia coli*"; (M. Ballantyne; Covance Laboratories Ltd., Harrogate, North Yorkshire HG3 1PY, England; Study No. 1849/8; 3/1/01); *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and *E.coli* WP2 uvrA were treated with AE C638206 00 1B99 0002 (batch no. R001737; purity: 99.3%) at concentrations ranging from 1.6 to 5000 µg/ml for 72 hours at 37^{o} 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 31.25 to 1000 ug/plate under conditions of +/- activation. In the activated samples the cells were preincubated with the test material for 1 hour 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, 4/20/07)

** 53014-0156; 232095; "AE C638206 00 1C96 0001 (OP 2050046): Reverse Mutation in Four Histidine-Requiring Strains of *Salmonella typhimurium* and One Tryptophan-Requiring Strain of *Escherichia coli*"; (M. Ballantyne; Covance Laboratories Ltd., Harrogate, North Yorkshire HG3 1PY, England; Study No. 1849/7; 3/1/01); *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and *E.coli* WP2 uvrA were treated with AE C638206 00 1C96 0001 (batch no. OP2050046; purity: 95.9%) at concentrations ranging from 1.6 to 5000 µg/ml for 72 hours at 37^{o} 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 31.25 to 1000 ug/plate under conditions of +/- activation. In the activated samples the cells were preincubated with the test material for 1 hour 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, 4/20/07)

** 53014-0157; 232096; "AE C638206 00 1C96 0002 (OP 2050045): Reverse Mutation in Four Histidine-Requiring Strains of *Salmonella typhimurium* and One Tryptophan-Requiring Strain of *Escherichia coli*"; (M. Ballantyne; Covance Laboratories Ltd., Harrogate, North Yorkshire HG3 1PY, England; Study No. 1849/6; 3/1/01); *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and *E.coli* WP2 uvrA were treated with AE C638206 00 1C96 0002 (batch no. OP2050045; purity: 95.6%) at concentrations ranging from 1.6 to 5000 µg/ml for 72 hours at 37^{o} 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 31.25 to 1000 ug/plate under conditions of +/- activation. In the activated samples the cells were preincubated with the test material for 1 hour 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, 4/20/07)

53014-0158; 232098; "AE C638206 00 1C99 0005: Reverse Mutation in Four Histidine-Requiring Strains of *Salmonella typhimurium* and One Tryptophan-Requiring Strain of *Escherichia coli*"; (M. Ballantyne; Covance Laboratories Ltd., Harrogate, North Yorkshire HG3 1PY, England; Study No. 1849/5; 3/1/01); *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and *E.coli* WP2 uvrA were treated with AE C638206 00 1C99 0005 (batch no. OP2050190, purity: not provided) at concentrations ranging from 1.6 to 5000 µg/ml for 72 hours at 37^{o} 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 31.25 to 1000 ug/plate under

conditions of +/- activation. In the activated samples the cells were preincubated with the test material for 1 hour 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 unacceptable**, possibly upgradeable with the submission of test material purity**.** (Moore, 4/23/07)

**** 53014-0159; 232099**; "AE C638206: Bacterial Reverse Mutation Test (including Amendment 2)"; (I. Stammberger; Aventis Pharma Deutschland GmbH, Drug Innovation & Approval, Lead Optimization, Drug Safety Evaluation, D-65926 Frankfurt am Main, Germany; Study No. Tox 99189; 9/14/00, amendment no. 2, 11/23/04); In Trial #1, *S. typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537 and *E. coli* strain WP2 uvrA were treated for 48 hours at 37^{o} C with AE C638206 technical (batch no. PP/241024/2 & PP/241067/1; purity: 97.8%) at concentrations ranging from 50 to 5000 ug/plate with and w/o activation using the plate incorporation procedure. Two additional assays were performed using the TA98 strain. In the 2nd trial, the range of concentrations were the same. However, the strains were perincubated with the test material for 20 minutes prior to plating. Each treatment level was plated in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was a treatment-related increase in the incidence of reverse mutation under conditions of activation for the TA98 strain. The positive controls were functional. **Possible adverse effect. Study acceptable.** (Moore, 4/23/07)

** 53014-0160; 232100; "AE C638206: *In Vitro* Mammalian Cell Gene Mutation Test (including Amendment 2)"; (I. Stammberger, H. Graeser; Aventis Pharma Deutschland GmbH, Drug Innovation & Approval, Lead Optimization, Drug Safety Evaluation, D-65926 Frankfurt am Main, Germany; Study No. TOX99190; 11/21/00, amendment no. 2, 1/6/05); Chinese Hamster lung V79 cells were treated with AE C638206 technical (batch no. PP/241024/2 & PP/241067/1; purity: 97.8%) at concentrations ranging from 1.2 to 3820 ug/ml in the 1st trial, from 0.4 to 120 ug/ml in the 2nd trial and from 0.313 to 60 ug/ml in the 3rd trial. The cells were exposed to the test material for 4 hours at 37^{o} C (precipitation of the test material was noted at concentrations $\geq$ 30 ug/ml). The assays were performed under both non-activated and activated conditions. A single culture was incubated for each treatment level. Five replicates/treatment level were subcultured with 6-thioguanine in the mutagenicity determination. Negative, vehicle, and positive control samples were cultured as well. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. No treatment-related increase in thioguanine-resistant cells was noted under condition of activation or non-activation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 4/24/07)

CHROMOSOME EFFECTS

**** 53014-0161; 232101**; "AE C638206: *In Vitro* Chinese Hamster Lung V79 Cells Chromosome Aberration Assay (including Amendment No. 1)"; (I. Stammberger, H. Graeser; Aventis Pharma Deutschland GmbH, Drug Innovation & Approval, Lead Optimization, Drug Safety Evaluation, D-65926 Frankfurt am Main, Germany; Study No. TOX99191; 12/14/00, amendment No. 1, 11/23/04); V79 Chinese hamster lung cells were exposed to concentrations of AE C638206 001C99 0005 (batch no. PP/241024/2 & PP241067/1; purity: 97.8%) ranging from 25.0 to 100.0 ug/ml under conditions of activation and non-activation for 3 hours and incubated for an additional 17 hours in the 1st trial. In the 2nd trial, the non-activated cultures were exposed to the test material for 20 hours. An Arochlor 1254-induced rat liver S9 fraction was used to metabolize the test material. Duplicate cultures were performed at each treatment level. One hundred metaphases per culture were evaluated (200 metaphases per treatment level) (only 100 metaphases per treatment level for the positive control samples). There was a treatment-related increase in chromosomal cell aberrations under conditions of both nonactivation and activation. Positive controls were functional. **Adverse effect indicated. Study acceptable.** (Moore, 4/24/07)

** 53014-0162; 232102; "AE C638206: *In Vitro* Mammalian Chromosome Aberration Test in Human Lymphocytes"; (L. Allais; Huntingdon Life Sciences Ltd., Alconbury, Huntingdon, Cambridgeshire, PE28 4HS, England; Project No. AES/031; 1/22/01); Primary human lymphocyte

cultures, procured from the whole blood of male volunteers (stimulated with PHA for 48 hours), were treated with concentrations of AE C638206 (lot no. OP2050046; purity: 95.9%) ranging from 4.88 to 625 ug/ml for 3 hours, followed by a recovery period of 18 hours of incubation under conditions of both nonactivation and activation in Trial No. 1. In Trial No. 2, the cells were treated with concentrations of the test material ranging from 1.22 to 625 ug/ml for 21 hours (nonactivation) or with 4.88 to 625 ug/ml of the test material for 3 hours, followed by a recovery period of 18 hours prior to being harvested (activation). An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. No treatment-related increase in chromosomal aberrations was evident under conditions either conditions of nonactivation or activation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 4/25/07)

DNA DAMAGE

** 53014-0163; 232103; "AE C638206: Induction of Micronuclei in the Bone Marrow of Treated Mice"; (J. Whitwell; Covance Laboratories Ltd., Harrogate, North Yorkshire HG3 1PY, England; Study No. 2014/70; 8/5/03); Six CD-1 male mice/group were dosed orally with 0 or 2000 mg/kg of AE C638206 (lot no. OP2050046; purity: 96.1%) twice, 24 hours apart, and euthanized 24 hours post-final dose. An additional 6 males were treated orally with the positive control (cyclophosphamide, 40 mg/kg) and euthanized 24 hours after dosing. Bone marrow samples from the femur were examined and the ratio of polychromatic (PCE) to normochromatic (NCE) and the percentage of PCE with a micronucleus were determined. No treatment-related increase in the number of PCE with a micronucleus was noted. **No adverse effect indicated. Study acceptable.** (Moore, 4/25/07)

** 53014-0164; 232104; "AE C638206: Micronucleus Test on the Male Mouse"; (B. Herbold; Bayer HealthCare AG, PH-PD P Health Care Toxicology, Molecular and Genetic Toxicology, D-42096 Wuppertal, Germany; Report No. C037549; 10/29/03); Five Hsd/Win male mice received two intraperitoneal (ip) injections with 0 (0.5% aqueous Cremophor), 150, 300 or 600 mg/kg of AE C638206; lot no. OP2350005; purity: 99.4%) 24 hours apart and were euthanized at 24 hours post-final dose. Five males received a single dose of 20 mg/kg of cyclophosphamide and were euthanized at 24 hours post-dose. The femoral bone marrow was harvested and evaluated for the presence of micronuclei in both polychromatic (PCE) and normochromatic erythrocytes (NCE). The number of NCE per 2000 PCE were evaluated per animal as well. Treatment-related signs included apathy, roughened fur, spasm, and difficulty breathing. There was no treatment-related increase in the number of micronuclei per 2000 PCE. The positive control was functional. **No adverse effect indicated. Study acceptable.** (Moore, 4/25/07)

** 53014-0165; 232105; "AE C638206: Mouse Erythrocyte Micronucleus Test"; (T. Roth; Aventis Pharma Deutschland GmbH, ProTox, 65795 Hattersheim, Germany; Study No. TOX99192; 10/31/00, amendment 2, 1/6/05); Five HsdWin:NMRI mice/sex/group received two oral doses of 0 (aqueous 1% methylcellulose), 200, 600 or 2000 mg/kg of AE C638206 (batch nos. PP/241024/2 & PP/241067/1, purity: 97.8%), 24 hours apart and were euthanized at 24 hours post-final dose. Five animals/sex received a single oral dose of Endoxan® (cyclophosphamide), 50 mg/kg and were euthanized at 24 hours post-dose. Bone marrow was harvested from the shafts of the femur. Two thousand polychromatic erythrocytes/animal were evaluated for the presence of micronuclei. In addition, the ratio of polychromatic erythrocytes to 200 normochromatic erythrocytes was determined. There was no treatment-related increase in the number of micronucleated polychromatic erythrocytes. The positive control was functional. **No adverse effect indicated. Study acceptable.** (Moore, 4/26/07)

** 53014-0166; 232106; "AE C638206: *In Vivo* Rat Liver Unscheduled DNA Synthesis (DNA Repair) Test (Including First Addendum)"; (C.E. Mason, J. Bright; Huntingdon Life Sciences Ltd., Alconbury, Huntingdon, Cambridgeshire, PE28 4HS, England; Addendum: Aventis CropScience UK Limited, Toxicology, Chesterford Park, Saffron Walden, Essex, CB10 1XL, England; Study No. TOX 99330; 11/9/00, Addendum, 11/15/00); Eight Sprague-Dawley male rats/group received a single oral dose of 0 (1% aqueous methylcellulose), 600 or 2000 mg/kg of AE C638206 technical (batch no. PP/241067/1 & PP/241024/2; purity: 97.7%) by gavage. Hepatocytes from 4

animals/group/time point were isolated at 2 and 14 hours post-dosing. Viability was determined by trypan blue dye exclusion and ranged from 55% to 91% for the animals treated with the test material. After attachment, cells were exposed to (methyl-^{3}H) thymidine for 4 hours followed by 24 hours with unlabelled thymidine. Three replicate cultures were performed per animal. Three slides per animal were scored, 50 cells per slide. No increase in the net nuclear grain counts was evident at any dose level or sampling time. **No adverse effect indicated**. Positive control was functional. **Study Acceptable**. (Moore, 4/26/07)

METABOLITES AND ANALOGUES

Gene Mutation

** 53014-0094; 226209; "AE 1344122 *Salmonella*/Microsome Test Plate Incorporation and Preincubation Method"; (B. Herbold; Bayer Health Care, Health Care Toxicology Molecular and Genetic Toxicology, Wuppertal, D-42096, Germany; Project ID T 5072079; 7/30/03); *S. typhimurium* TA98, TA100, TA102, TA1535 and TA1537 strains were incubated with AE 1344122 (batch no. YG3228, purity: 98.8%) 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 apparent treatment-related increase in the incidence of reverse mutation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 12/18/06)

** 53014-0096; 226211; "AE C657378 *Salmonella*/Microsome Test Plate Incorporation and Preincubation Method"; (B. Herbold; Bayer HealthCare, Health Care Toxicology Molecular and Genetic Toxicology, Wuppertal, D-42096, Germany; Project ID. T 2063319; 8/26/03); *S. typhimurium* TA98, TA100, TA102, TA1535 and TA1537 strains were incubated with AE C657378 (batch no. 1119-DC/3, purity: 98.3%) 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 cultured in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. Precipitation of the test material was evident at 1581 ug/plate and above in selected cultures. No inhibition of growth was observed. 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, 12/19/06)

** 53014-0097; 226212; "Bacterial Mutation Assay AE C657188 (Plant Metabolite of AE C638206)"; (J. Kitching; Huntingdon Life Sciences Ltd., Huntingdon, Cambridgeshire PE28 4HS, England; Project ID. Tox 20045; 9/14/00); In the first trial, *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 and *E. coli* WP2*uvr*A/pK101 (CM891) were exposed to AE C657188 (batch no. R001739, purity: 99.7%) at concentrations ranging from 5 to 5000 ug/plate for 72 hours at 37° C, using the plate incorporation technique. In the 2nd trial, the same strains were exposed to concentrations of the test material ranging from 50 to 5000 ug/plate for 30 minutes at 37° during a pre-incubation period followed by exposure for 72 hours at 37° C. Both trials were performed under conditions of non-activation and activation. There were 3 plates per treatment level. An S9 fraction derived from the liver of rats pretreated with Aroclor 1254 was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. **No adverse effect indicated.** The positive controls were functional. **Study acceptable.** (Moore, 12/20/06)

** 53014-0098; 226213; "Evaluation of the Possible Mutagenic Activity of 2,6-Dichlorobenzamide in the Ames *Salmonella*/Microsome Test"; (J. Koom; Solvay Duphar B.V., Weesp, 1381 CP, Netherlands; Project ID. 56645/69/92; 10/20/93); *S. typhimurium* TA98, TA100, TA1535 and TA1537 strains were incubated with 2,6-Dichlorobenzamide (batch no. FUX001000/FUN81G02C, purity: 100%) at levels ranging from 625 to 5000 µg/plate (both trials) under conditions of (-/+) activation and incubated for 72 hours at 37° C by means of the plate incorporation method. Each treatment was cultured in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to

metabolize 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, 12/20/06)

** 53014-0099; 226214; "*Salmonella*/Microsome Test Plate Incorporation and Preincubation Method"; (B. Herbold; Bayer HealthCare Ag, Health Care Toxicology Molecular and Genetic Toxicology, Wuppertal, D-42096, Germany; Project ID. AT00853; 12/10/03); *S. typhimurium* TA98, TA100, TA102, TA1535 and TA1537 strains were incubated with AE C653711 (batch no. 08018ET; purity: 96.2%) 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 cultured in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize 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, 12/21/06)

** 53014-0100; 226215; "AE 1C657188 V79/HPRT - Test *in Vitro* for the Detection of Induced Forward Mutations"; (B. Herbold; Bayer HealthCare, Health Care Toxicology Molecular and Genetic Toxicology, Wuppertal, D-42096, Germany; Project ID. T 8072081; 7/16/03); Chinese hamster V79 cells were exposed to AE C657188 (batch no. D0526=OP2150091, purity: 97.7% (analysis: 2/18/03)) at concentrations ranging from 16 to 5000 µg/ml in the 1st trial and from 16 to 4000 in the 2nd trial for 5 hours at 37° C with and w/o activation. Each treatment level was cultured in duplicate. 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, 12/22/06)

** 53014-0101; 226216; "AE 1344122 Metabolite of AE C638206 V79/HPRT - Test *in Vitro* for the Detection of Induced Forward Mutations"; (B. Herbold; Bayer HealthCare, Health Care Toxicology Molecular and Genetic Toxicology, Wuppertal, D-42096, Germany; Project ID. T 7072080; 7/28/03); Chinese hamster V79 cells were exposed to AE 1344122 (batch no. YG3228, purity: 98.8%) at concentrations ranging from 75 to 2400 µg/ml for 5 hours at 37° C 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, 12/22/06)

** 53014-0102; 226217; "AE C653711 Metabolite of AE C638206 V79/HPRT - Test *in Vitro* for the Detection of Induced Forward Mutations"; (B. Herbold; Bayer HealthCare, Health Care Toxicology Molecular and Genetic Toxicology, Wuppertal, D-42096, Germany; Project ID. T4072078; 8/5/03); Chinese hamster V79 cells were exposed to AE C653711 (batch no. 08018 ET; purity: 96.2%) at concentrations ranging from 125 to 5000 µg/ml for 5 hours at 37° C with and w/o activation. Two trials were performed with duplicate cultures for each treatment level. A third trial was performed with activation due to low cell survival and/or problems with contamination in the first two trials. 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, 12/26/06)

** 53014-0103; 226218; "AE C657378 V79/HPRT - Test *in Vitro* for the Detection of Induced Forward Mutations"; (B. Herbold; Bayer HealthCare, Health Care Toxicology Molecular and Genetic Toxicology, Wuppertal, D-42096, Germany; Project ID. T4063320; 8/25/03); Chinese hamster V79 cells were exposed to AE C657378 (batch no. 1119-DC/3; purity: 98.3%) at concentrations ranging from 550 to 4400 µg/ml for 5 hours at 37° C 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, 12/27/06)

** 53014-0095; 226210; "AE C638206 SC 480 *Salmonella*/Microsome Test Plate Incorporation and Preincubation Method"; (B. Herbold; Bayer HealthCare Ag, Toxicology International Toxicology Molecular and Genetic Toxicology, Wuppertal, D-42096, Germany; Project ID. AT01151; 4/20/04);
S. typhimurium TA98, TA100, TA102, TA1535 and TA1537 strains were incubated with AE C638206 SC 480 (batch no. OP220823; a.i.: 487 g/l) 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 cultured in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize 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, 12/19/06)

Chromosome Effects

** 53014-0104; 226219; "AE 1344122 (Metabolite of AE C638206) Induction of Chromosome Aberrations in Cultured Human Peripheral Blood Lymphocytes"; (M. Lloyd; Covance Laboratories Ltd., North Yorkshire, HG3 1PY, England; Project ID. 2014/67; 7/1/03); Phytohemogglutinin treated human lymphocytes (whole blood) were treated with AE 1344122 (Metabolite of AE C638206) (batch no. YG3228; purity: 98.8%) at concentrations ranging from 57.02 to 2532 ug/ml in the 1st trial under conditions of both non-activation and activation and from 221.2 to 2532 ug/ml under conditions of non-activation and from 811.7 to 2532 ug/ml under conditions of activation in the 2nd trial. The incubations were performed at 37° C. In the 1st trial, under conditions of both non-activation and activation, the cells were exposed to the test material for 3 hours, washed and then incubated for an additional 17 hours. In the 2nd trial, in the non-activated assay, the cells were exposed to the test material for 20 hours. The cells in the activated assay were treated in the same manner as in the 1st trial. A liver homogenate S9 fraction from male rats pretreated with Aroclor 1254 was used to metabolize the test material. There was no increase in the incidence of chromosomal aberrations under conditions of activation or non-activation. **No adverse effect indicated.** The positive controls were functional for both activation and non-activation. **Study acceptable.** (Moore, 12/27/06)

**** 53014-0105; 226220**; "AE C657378: Induction of Chromosome Aberrations in Cultured Human Peripheral Blood Lymphocytes"; (T.S. Kumaravel; Covance Laboratories Ltd., North Yorkshire, HG3 1PY, England; Project ID. 2014/69; 11/14/03); Phytohemogglutinin treated human lymphocytes (whole blood) were treated with AE C657378 (2,6-dichloro-3-hydroxybenzamide); (batch no. 1119-DC/3, purity: 98.3%) at concentrations ranging from 154.7 to 2060 ug/ml in the 1st trial and from 276.5 to 2060 ug/ml in the 2nd trial under conditions of non-activation and from 869.1 to 2060 ug/ml under conditions of activation at 37° C (only one trial was performed). In the 1st trial, under conditions of non-activation, the cells were exposed to the test material for 20 hours. Under conditions of activation (1st trial) and the non-activation assay in the 2nd trial, the cells were exposed to the test material for 3 hours, washed and then incubated for an additional 17 hours. A liver homogenate S9 fraction from male rats pretreated with Aroclor 1254 was used to metabolize the test material. There was an increase in the incidence of chromosomal aberrations under conditions of non-activation with 20 hours of treatment. **Adverse effect indicated.** The positive controls were functional for both activation and non-activation. **Study acceptable.** (Moore, 12/27/06)

** 53014-0106; 226221; "AE C657188 (Metabolite of AE C638206): Induction of Chromosome Aberrations in Cultured Human Peripheral Blood Lymphocytes"; (M. Lloyd; Covance Laboratories Ltd., North Yorkshire, HG3 1PY, England; Project ID. 2014/68; 7/1/03); Phytohemogglutinin-treated human lymphocytes (whole blood) were treated with AE C657188 (metabolite of AE C638206) (batch no. OP2150091, purity: 99.1%) at concentrations ranging from 50.80 to 2256 ug/ml in the 1st trial under conditions of both non-activation and activation and in the 2nd trial from 272.8 to 2256 ug/ml under conditions of non-activation and from 522.5 to 2256 ug/ml under conditions of activation at 37° C. In the 1st trial, under conditions of both non-activation and activation, the cells were exposed to the test material for 3 hours, washed and then incubated for

an additional 17 hours. In the 2nd trial, in the non-activated assay, the cells were exposed to the test material for 20 hours. The cells in the activated assay were treated in the same manner as in the 1st trial. A liver homogenate S9 fraction from male rats pretreated with Aroclor 1254 was used to metabolize the test material. Precipitation of the test material was noted at 1805 ug/ml and above for the 1st trial and from 723.2 ug/ml and above for the non-activated samples and from 1385 ug/ml and above for the activated assay in the 2nd trial. There was no increase in the incidence of chromosomal aberrations under conditions of activation or non-activation. **No adverse effect indicated.** The positive controls were functional for both activation and non-activation. **Study acceptable.** (Moore, 12/29/06)

DNA Damage

** 53014-0107; 226222; "AE C657378 Micronucleus - Test on the Male Mouse"; (B. Herbold; Bayer HealthCare AG, Health Care Toxicology Molecular and Genetic Toxicology, Wuppertal, D-42096, Germany; Project ID. T 3072950; 11/28/03); Five male Hsd/Win mice/group were dosed twice by intraperitoneal (ip) injection with 0, 300, 600 or 1200 mg/kg of AE C657378 (batch no. 1119-DC/3, purity: 98.3%) with a 24 hour interval between injections (note: an additional group of 5 males were treated with 1200 mg/kg twice as a reserve). The animals were euthanized 24 hours after the second injection. The vehicle was 0.5% aqueous Cremophor. 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. One thousand polychromatic erythrocytes were evaluated per animal. One of the 1200 mg/kg animals died. Treatment-related signs included apathy, roughened fur, lateral recumbency, spasms and difficulty 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, 12/29/06)

** 53014-0108; 226224; "AE C657378 (Project AE C638206) Unscheduled DNA Synthesis Test with Rat Liver Cells *in Vivo*"; (S. Brendter-Schwaab; Bayer HealthCare AG, Toxicology International Molecular and Genetic Toxicology, Wuppertal, D-42096, Germany; Project ID. T3073210; 4/28/04); Eight Sprague-Dawley male rats/group received a single oral dose of 0 (aqueous 0.5% cremophor), 1000 or 2000 mg/kg of AE C657378 (batch no. 1119-DC/3, purity: 98.3%) by gavage. Hepatocytes from 4 animals/group/time point were isolated at 4 and 16 hours post-dosing. Viability was determined by trypan blue dye exclusion and ranged from 71.6% to 81.3%. After attachment, cells were exposed to (methyl-^{3}H) thymidine for 4 hours followed by an overnight incubation with unlabelled thymidine. Three slides per animal were scored, 50 cells per slide. No increase in the net nuclear grain counts was evident at any dose level or sampling time. **No adverse effect indicated**. Positive controls were functional. **Study Acceptable**. (Moore, 1/2/07).

** 53014-0126; 226244; "AE C638206 SC 480 Micronucleus-Test on the Male Mouse"; (B. Herbold; Bayer HealthCare AG, Toxicology International Molecular and Genetic Toxicology, Wuppertal, D-42096, Germany; Project ID. T 8073224; 4/2/04); Five male Hsd/Win mice/group were dosed twice by intraperitoneal (ip) injection with 0, 200, 400 or 800 mg/kg of AE-C638206 SC 480 (batch no. OP220823; a.i.: 487 g/l) with a 24 hour interval between injections (note: an additional group of 5 males were treated with 800 mg/kg twice as a reserve). The animals were euthanized 24 hours after the second injection. The vehicle was distilled water. 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. One thousand polychromatic erythrocytes were evaluated per animal. Treatment-related signs included apathy, roughened fur, sternal recumbency, 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, 1/12/07)

NEUROTOXICITY

No studies submitted nor required at this time.

SUBCHRONIC STUDIES

Rat 4-Week Dietary Toxicity Study

53014-0087; 226202; "Rat 28-day Dietary Toxicity Study AE C638206 Code: AE C638206 00 1C99 0003"; (P. Higgs; Aventis CropScience UK Limited Laboratory, Chesterford Park, Saffron, Walden, Essex, CB10 1XL, England; Project ID. TOX/00/283-1; 7/27/00); Five Sprague-Dawley rats/sex/group received 0, 20, 200, 2000 or 20000 ppm of AE C638206 (batch no. CDB234167-2, purity: 99.9%) in the diet for 4 weeks ((M) 0, 1.74, 17.4, 174, 1720 mg/kg/day, (F) 0, 1.81, 17.9, 184, 1820 mg/kg/day). No deaths resulted from the treatment. The mean body weights and food consumption of both sexes in the 20000 ppm group were lower than the control values during the first week of the treatment. The body weights of both sexes in this group were lower than those of the control throughout the remainder of the study even though the food consumption of these animals recovered during the second week. In the FOB, the mean rectal body temperatures of both sexes in the 20000 ppm group were lower than those of the controls on day 2 of the study ($p<0.01$ or 0.05). No effect on the body temperature was evident in later measurements. Although numerous hemoglobin parameters for the males in the treated groups were statistically different from those of the control, a dose-effect relationship was not apparent and the mean values for the treated animals were within historical control ranges. In the clinical chemistry evaluation, the mean creatinine and cholesterol values of both sexes in the 20000 ppm group were elevated ($p<0.01$ or 0.001). The mean cholesterol values for both sexes in the 2000 ppm group were increased as well ($p<0.01$). The mean absolute and relative liver weights for the males in the 20000 ppm group and the relative liver weights for the 20000 ppm females were greater than the control values ($p<0.05$ or 0.01). The mean absolute and relative spleen weights for the 2000 and 20000 ppm males were less than the those of the controls ($p<0.05$ or 0.01). The mean absolute spleen weight for the 20000 ppm females was less than that of the control ($p<0.05$). In the histological examination, no lesions were evident in the spleen. In the liver, centrilobular hepatocytic hypertrophy was noted for both sexes in the 200 ppm groups and above ((M) 0: 0/5 vs. 200: 2/5, 2000: 5/5, 20000: 5/5, (F) 0: 0/5 vs. 200: 3/5, 2000: 2/5, 20000: 5/5). In the kidneys of the 2000 and 20000 ppm males, an increased severity of phloxine tartrazine positive granulation was evident (0: 4 minimal, 1 moderate vs. 2000: 3 moderate, 2 severe, 20000: 1 slight, 3 moderate, 1 severe). Hydronephrosis was noted in kidneys of two males in the 20000 ppm group in contrast to none of the males in the control group being affected. Tubular eosinophilic proteinaceous material was noted in the kidneys of males of all of the treated groups (0: 0/5 vs. 20: 2/5 (1 minimal, 1 slight), 200: 4/5 (3 minimal, 1 slight), 2000: 5/5 (1 slight, 4 moderate), 20000: 1 minimal, 3 slight, 1 severe). **No adverse effect indicated.** Target organs: liver and kidneys; **4-Week Dietary NOEL:** (M/F) 20 ppm ((M) 1.74 mg/kg/day, (F) 1.81 mg/kg/day) (based upon the incidence of lesions in livers of both sexes in the 200 ppm group). **Study supplemental** (non-guideline study). (Moore, 12/12/06)

Rat Subchronic Dietary Toxicity Study

53014-0137; 230017; "AE C638206: Rat 90-Day Dietary Toxicity Study with a 4 Week Off-Dose Period"; (B.A. Mallyon; Aventis CropScience UK Limited, Toxicology, Chesterford Park, Saffron Walden, Essex, CB10 1 XL, England; Study No. TOX 99198; 12/1/00); Ten Sprague-Dawley rats/sex/group received 0, 100, 1400 and 20000 ppm of AE C638206 (no batch no., purity: 96.9% (6/10/99), 97.5% (8/16/99)) in the diet for 13 weeks ((M) 0, 7.4, 109, 1668 mg/kg/day, (F) 0, 8.4, 119, 1673 mg/kg/day). Additional ten animals/sex/group in the control and 20000 ppm groups were dosed for the 13 weeks and then retained for a 4-week recovery period. The mean body weights of both sexes in the 20000 ppm group and the males in the 1400 ppm group were less than those of the control through out the study ($p<0.05$ or NS). The mean body weights of both sexes in the 20000 ppm group had not fully recovered by the end of the 4-week recovery period ($p<0.05$). The mean food consumption of both sexes in the 20000 ppm group was less than that of the control through out the study ($p<0.05$). No treatment-related effects were noted in the ophthalmological examination and urinalysis. In the hematology evaluation, the hemoglobin and hematocrit levels of both sexes in the 20000 ppm group and the males in the 1400 ppm group were lower than those values for the controls ($p<0.001$, 0.01 or 0.05). The MCH

and the MCHC of both sexes in the 20000 ppm group and the MCV of the 20000 ppm females were lower than those values of the control as well ($p<0.01$ or 0.001). The APPT value of the 20000 ppm males was longer than that of the control group ($p<0.001$). No treatment-related effects on the hematology parameters were evident in the recovery group. In the clinical chemistry evaluation, the total protein and total globulin in the serum of both sexes in the 20000 ppm group and the albumin of the 20000 ppm males were greater than the control values ($p<0.01$ or 0.001). The creatinine level of both sexes in the 20000 ppm group and of the males in the 1400 ppm group was greater than that of the control ($p<0.001$ or 0.05). The urea in the serum of the males in the 20000 ppm group was increased as well ($p<0.05$). The serum glucose level was lower in the males of the 20000 ppm group ($p<0.01$). The mean serum cholesterol levels of the 100 ppm males and above and of the 20000 ppm females were greater than the values for the control animals ($p<0.05$ or 0.001). No treatment-related effects on the clinical chemistry parameters were evident in the recovery group. In the necropsy examination, the mean relative liver weights of both sexes in the 20000 ppm group and of the males in the 1400 ppm group were greater than the control values ($p<0.05$). This effect persisted for both sexes in the 20000 ppm group through the 4-week recovery period ($p<0.05$). The mean relative kidney weights of the 1400 and 20000 ppm males were greater than that of the control ($p<0.05$). This effect did not persist in the recovery group. In the histopathological examination, the incidence of hypertrophy of the zona glomerulus of the adrenal cortex of both sexes in the 20000 ppm group and of the females in the 1400 ppm group was increased ((M) 0: 1/10 vs. 20000: 7/10, (F) 0: 1/10 vs. 1400: 3/10, 20000: 10/10). Decreased cellularity was noted in the bone marrow of both sexes in the 20000 ppm group ((M) 0: 0/10 vs. 20000: 7/10, (F) 0: 3/10 vs. 20000: 9/10). Trabecular hyperostosis was noted in the femur joint of both sexes in the 20000 ppm group and of the females in the 1400 ppm group ((M) 0: 0/10 vs. 20000: 7/10, (F) 0: 3/10 vs. 1400: 8/10, 20000: 9/10). An increased severity and incidence of effects was noted in the kidneys of the males in the 1400 and 20000 ppm groups. These effects included the accumulation of hyaline droplets in the proximal tubule and single cell death in the proximal tubule epithelium. Hypertrophy of the centrilobular hepatocytes of the liver was noted for both sexes in the 20000 ppm group and for the males in the 1400 ppm group ((M) 0: 0/10 vs. 1400: 8/10, 20000: 9/10, (F) 0: 0/10 vs. 20000: 8/10). Axonal degeneration of the optic nerve was noted for the three males in the 20000 ppm group with no control males exhibiting the lesion. One control female exhibited the same lesion. For the 20000 ppm recovery group, the hypertrophy of the zona glomerulosa in the adrenal gland was still evident for both sexes ((M) 0: 0/10 vs. 20000: 8/10, (F) 0: 1/10 vs. 20000: 5/10). Decreased cellularity was minimal in the bone marrow of 3 males in the 20000 ppm group and 4 females in the control and 2 females of the 20000 ppm group. Another 3 females in the 20000 ppm recovery group exhibited slight decrease in cellularity of the marrow. An increased incidence of trabecular hyperostosis of the femur joint was still noted in the 20000 ppm group females after the 4-week recovery (0: 1/10 vs. 20000: 7/10). **Possible adverse effect:** decreased cellularity in the bone marrow and increased trabecular hyperostosis in the femur joint; **Rat Subchronic Dietary Toxicity NOEL:** (M/F) 100 ppm ((M): 7.4 mg/kg/day, (F) 8.4 mg/kg/day) (based upon the treatment-related effects on the kidneys, liver, adrenal cortex, bone marrow and/or bone joints of both sexes in the 1400 ppm group); **Study acceptable.** (Moore, 1/30/07)

Rat 4-Week Repeated Dosing Dermal Toxicity Study

53014-0091; 226206; "A Subacute Dermal Toxicity in Rats with AE C638206"; (E.A. Eigenberg, B.P. Stuart; Bayer CropScience LP, Stilwell, KS 66085; Project ID. 200705; 9/17/03); The skin of ten Wistar rat/sex/group was exposed to 0, 100, 250, 500 or 1000 mg/kg/day of AE C638206 (batch no. 2050190/PP241024/2; purity: 97.7%), 6 hours/day, 5 days/week for 4 weeks. The test material was moistened with aqueous 0.5% carboxmethylcellulose. No deaths resulted from the treatment. There was no treatment-related effects upon either the mean body weights or the food consumption. The hematology, clinical chemistry and histopathological evaluations did not reveal any treatment-related effects. **No adverse effect indicated.** No localized dermal irritation was evident at the site of application for the highest treatment level. **21/28-Day Dermal Toxicity NOEL:** (M/F) 1000 mg/kg/day (based upon the lack of treatment-related effects at the highest treatment level); **Study acceptable.** (Moore, 12/15/06)

Mouse 4-Week Dietary Toxicity Study

53014-0086; 226201; "Mouse 28-day Dietary Toxicity Study AE C638206 Code: AE C638206 00 1C99 0004"; (B.A. Mallyon; Aventis CropScience UK Limited Laboratory, Chesterford Park, Saffron, Walden, Essex, CB10 1XL, England; Project ID. TOX/00/283-2; 11/24/00); Five CD-1 mice/sex/group received 0, 6, 64, 640 or 6400 ppm of AE C638206 (batch no. CDB234187-1, purity: 99.0%) in the diet for 28 days ((M) 0, 0.95, 10.4, 100, 980 mg/kg/day, (F) 0, 1.19, 12.9, 129, 1242 mg/kg/day). No deaths resulted from the treatment. There were no apparent treatment-related effects upon the mean body weights or food consumption. No apparent treatment-related effects were noted in the hematology data. The mean serum albumin levels were decreased for both sexes in the 6400 ppm group and for females in the 640 ppm group ($p<0.01$). The mean serum globulin levels were increased for both sexes in the 6400 ppm group. The A/G ratio was decreased for both sexes in the 6400 ppm group ($p<0.001$). The alanine aminotransferase activity in the serum was increased in a dose-related manner for both sexes in the 640 and 6400 ppm groups ($p<0.01$ or 0.001). Although other parameters appeared to be affected by the treatment, no dose-related effect was apparent. In the necropsy examination, the mean absolute and relative liver weights of both sexes in the 6400 ppm group were increased over those of the control ($p<0.01$). The mean relative liver weight of the 640 ppm females was greater than that of the controls, as well ($p<0.01$). The histological examination of the liver revealed an increased incidence and severity of centrilobular hepatocellular hypertrophy for both sexes in the 640 and 6400 ppm groups ((M) 0: 3/5 (3 minimal) vs. 640: 5/5 (1 minimal, 3 slight, 1 moderate, 6400: 5/5 (1 slight, 4 moderate), (F) 0: 1/5 (1 minimal) vs. 640: 4/5 (1 minimal, 3 slight), 6400: 5/5 (5 moderate). **No adverse effect evident.** Target tissue: liver; **4-Week Dietary NOEL:** 64 ppm ((M) 10.4 mg/kg/day, (F) 12.9 mg/kg/day) (based upon the increased incidence and severity of lesions in the liver of both sexes in the 640 ppm group); **Study supplemental** (non-guideline study). (Moore, 12/11/06)

Mouse Subchronic Dietary Toxicity Study

53014-0138; 230018; "AE C638206: Mouse 90-Day Dietary Toxicity Study"; (B.A. Mallyon; Aventis CropScience UK Limited, Toxicology, Chesterford Park, Saffron Walden, Essex, CB10 1 XL, England; Study No. TOX 99216; 9/6/00); Ten CD-1 mice/sex/group received 0, 32, 320, 3200 or 6400 ppm of AE C638206 (no batch no.; purity: 96.9% (6/10/99), 97.3% (8/16/99)) in the diet for 13 weeks ((M) 0, 4.7, 46, 461, 944 mg/kg/day, (F) 0, 6.2, 60, 629, 1239 mg/kg/day). No deaths resulted from the treatment. The mean body weights of both sexes in the 6400 ppm group and the females in the 3200 ppm group were less the control values over the course of the study (NS). The mean body weight gain and mean food consumption were reduced for the males in all of the treatment groups during the 1st week of the study, returning to control levels by the 2nd week ($p<0.05$ or NS). In the hematology evaluation, the hemoglobin concentration of the 6400 ppm females was lower than that of the control ($p<0.05$). In the clinical chemistry, the total serum globulin levels were increased for both sexes in the 6400 ppm group and for the males in the 3200 ppm group ($p<0.05$ or 0.01). The serum albumin levels were decreased for the treated animals in comparison with the controls. However, a treatment-related response was not evident. The creatinine concentrations for both sexes in the 6400 ppm group and for the 3200 ppm females were greater than the control values ($p<0.001$). The AST and ALT activities in the serum were elevated for the males in both the 3200 and 6400 ppm groups ($p<0.05$, 0.01, or 0.001). The ALT activity of the 6400 ppm females and the AP activity of the 6400 ppm males were elevated as well ($p<0.01$ or 0.001). The mean absolute and relative liver weights of both sexes in the 3200 and 6400 ppm groups were greater than the control values ($p<0.05$). In the histopathological examination, the incidence and severity of centrilobular hepatocytic hypertrophy was increased for both sexes in the 320 ppm group and above ((M) 0: 0/10 vs. 320: 9/10, 3200: 10/10, 6400: 10/10, (F) 0: 1/10 vs. 320: 2/10, 3200: 9/10, 6400: 10/10). Focal hepatic necrosis was noted in the livers of the 3200 and 6400 ppm males ((M) 0: 0/10 vs. 3200: 1/10, 6400: 3/10). Target organ: liver; **Possible adverse effect::** focal hepatocytic necrosis in the liver; **Mouse Subchronic Dietary Toxicity NOEL:** (M/F) 32 ppm ((M) 4.7 mg/kg/day, (F) 6.2 mg/kg/day) (based upon the centrilobular hepatocytic hypertrophy noted in the livers of both sexes in the 320 ppm group); **Study supplemental** (study did not fulfill all of the subchronic dietary toxicity study requirements). (Moore, 1/31/07)

53014-0139; 230019; "AE C638206: 90-Day Toxicity Study in the Mouse by Dietary Administration"; (S. Wason; Aventis CropScience, F-06903 Sophia Antipolis Cedex, France; Study No. SA 00363; 7/20/01); Ten C57BL/6JICO mice/sex/group received 0, 50, 200, 800 or 3200 ppm of AE C638206 technical (batch no. OP2050046, purity: 95.9%) in the diet for 13 weeks ((M) 0, 10.4, 37.8, 160.7, 770.2 mg/kg/day, (F) 0, 12.6, 52.8, 207.3, 964.9 mg/kg/day). There were no deaths which were considered to be treatment-related during the study. However, two males in the control, one in the 200, two in the 800 and two in the 3200 ppm groups and one female each in the control, 50 and the 800 ppm groups died during the study. The mean body weights of both sexes in the 3200 ppm group were less than the control during the first weeks of the study ($p<0.05$). By the termination of the study, no effect on the body weights was evident. Excessive spillage of the food at various times during the study affected the accuracy of the food consumption measurements. In the clinical chemistry evaluation, the mean serum albumin levels of both sexes in the 800 and 3200 ppm groups were lower than those of the control ($p<0.01$). The mean absolute and relative liver weights of both sexes in the 3200 ppm group and of the females in the 800 ppm group were greater than the control values ($p<0.05$ or 0.01). The mean relative liver weights for the 800 ppm males were greater than that of the controls as well ($p<0.01$). In the histopathological examination, hypertrophy of the centrilobular hepatocytes in the liver was noted for both sexes in the 800 and 3200 ppm groups ((M) 0: 0/8 vs. 800: 4/8, 3200: 8/8, (F) 0: 0/9 vs. 800: 8/9, 3200: 10/10). Multifocal single cell necrosis was also noted in the livers of the 3200 ppm males (0: 0/8 vs. 3200: 4/8). Target organ: liver; **Possible adverse:** multifocal single cell necrosis in the liver; **Mouse Subchronic Dietary Toxicity NOEL:** (M/F) 200 ppm ((M) 37.8 mg/kg/day, (F) 52.8 mg/kg/day) (based upon the increased liver weight and hepatocellular hypertrophy noted for both sexes in the 800 ppm group). **Study supplemental** (non-guideline study). (Moore, 2/2/07)

Dog 4-Week Oral Toxicity Study

53014-0090; 226205; "AE C638206 Dog 28-day Oral Toxicity Study"; (B.A. Mallyon; Aventis CropScience UK Limited Laboratory, Chesterford Park, Saffron, Walden, Essex, CB10 1XL, England; Project ID. TOX/00/283-3; 10/5/00); Two beagle dogs/sex/group received 0, 10, 100 or 1000 mg/kg/day of AE C638206 (batch no. PP241024/2 & PP241067/1, purity: 96.9%) for 4 weeks. With an N of 2/sex, the data were not sufficient to establish any treatment-related effects for the mean body weights, food consumption, hematology, clinical chemistry, urinalysis, necropsy and histopathological evaluations. The study results demonstrate that the dog can endure a limit treatment of 1000 mg/kg/day. **No adverse effect indicated. NOEL** not assigned due to insufficient numbers of animals. **Study supplemental** (non-guideline study). (Moore, 12/15/06)

Dog Subchronic Oral Toxicity Study

53014-0140; 230020; "AE C638206: Dog 90-day Oral Toxicity Study"; (B.A. Mallyon; Aventis CropScience UK Limited Laboratory, Chesterford Park, Saffron, Walden, Essex, CB10 1XL, England; Study No. TOX 99292; 12/5/00); Four beagle dogs/sex/group were dosed orally by gavage with 0, 5, 70 or 1000 mg/kg/day of AE C638206 technical (batch no. PP241024/2 & PP241067/1; purity: 97.7%) for 13 weeks. The test material was suspended in aqueous 1% (w/v) methyl cellulose. All of the study animals survived to the termination of the study. The mean body weight gain of both sexes in the 1000 mg/kg group was less than that of the control group (NS). The mean food consumption of the females in the 1000 mg/kg group was less than that of the control throughout the study (NS). The ophthalmology, hematology and urinalysis evaluations did not reveal any treatment-related effects. In the clinical chemistry evaluation, The serum alkaline phosphatase activity was elevated for both sexes in the 1000 mg/kg group over the course of the study (NS or $p<0.05$). The total bilirubin concentration was lower for the males in the 1000 mg/kg group over the course of the study ($p<0.01$ or 0.05). The absolute liver weight of the 1000 mg/kg males and the relative liver weights of both sexes in the 1000 mg/kg group were greater than the control values ($p<0.05$). In the histopathological evaluation, slight centrilobular hepatocytic lipid was noted in the livers of two males in the 1000 mg/kg group. Target organ: liver; **No adverse effect indicated. Dog Subchronic Oral Toxicity NOEL:** (M/F) 70 mg/kg/day (based upon the increased absolute and/or relative liver weights of both sexes and the incidence

of lipid in the hepatocytes of the males in the 1000 mg/kg treatment group). **Study acceptable.** (Moore, 2/2/07)

METABOLITES AND ANALOGUES

AE 1344122: Rat 4-Week Dietary Toxicity Study

53014-0088; 226203; "AE 1344122 28-day Toxicity Study in the Rat by Dietary Adminstration"; (A. McElligott; Bayer CropScience, Sophia Antipolis Cedex, F-06903, France; Project ID. SA 03054; 10/3/03); Ten Wistar rats/sex/group received 0, 20, 200, 2000 or 20000 ppm of AE 1344122 (batch no. YG3228; purity: 98.8%) in the diet for 4 weeks ((M) 0, 1.5, 14.9, 151.6, 1495 mg/kg/day, (F) 0, 1.7, 16.8, 167.1, 1616 mg/kg/day). No deaths resulted from the treatment. The mean body weight of the 20000 ppm males was less than that of the controls after 4 weeks of treatment ($p<0.01$). The mean food consumption of both sexes in the 20000 ppm group was less than that of the controls in the first week of treatment ($p<0.05$ or 0.01). The neurotoxicity evaluation did not reveal any treatment-related effects. No treatment-related effect was evident in the hematology, clinical chemistry or ophthalmological evaluations. In the urinalysis, the pH of the urine of both sexes in the 20000 ppm group was less than that of the controls ($p<0.05$, NS). Casts were noted in the urine of 9 of 10 females in the 20000 ppm group as compared to none of the control females. The organ weights were not affected in a treatment-related manner. In the histopathological evaluation, tubular generation/regeneration and single cell necrosis was noted in the kidneys of 8 females of the 20000 ppm group as compared to none of the females in the control group exhibiting these lesions. The kidneys of two females in the 20000 ppm group demonstrated mineralization of the papillae. **Possible adverse effect:** single cell necrosis in the kidney; target organ: kidney. **4-Week Dietary Toxicity NOEL:** 2000 ppm ((M) 151.6 mg/kg/day; (F) 167.1 mg/kg/day) (based upon the lower mean body weight for the males and the lesions in the kidneys of the females in the 20000 ppm group); **Study supplemental** (non-guideline study). (Moore, 12/13/06)

AE C657378: Rat 4-Week Dietary Toxicity Study

53014-0089; 226204; "AE C657378 Subacute Toxicity in Rats in the Diet for 4 Weeks"; (R. Eiben, M. Rinke; BHC PH-PD-P-HC Toxicology Experimental Toxicology, Wuppertal, D42096, Germany; Project ID. T1072327; 9/19/03); Ten Wistar rats/sex/group received 0, 20, 200, 2000 or 20000 ppm of AE C657378 (batch no. 1119-DC/3; purity: 98.3%) in the diet for 4 weeks (IM) 0, 1.6, 16.2, 159.2, 1775 mg/kg/day, (F) 0, 2.1, 20.4, 230.6, 1931 mg/kg/day). No deaths resulted from the treatment. The mean body weights of the 20000 ppm males were less than those of the control during the last two weeks of the study ($p<0.05$ or 0.01). The mean food consumption of the 20000 ppm females was less than that of the controls throughout the study ($p<0.05$ or NS). No treatment-related effects were evident in the FOB evaluations. The ophthalmological examination and hematology evaluation did not reveal any treatment-related effects. In the clinical chemistry evaluation, the mean cholesterol values of both sexes in the 20000 ppm group were greater than those of the control ($p<0.05$ or 0.01). The mean serum calcium values were increased for both sexes in the 20000 ppm group and for the males in the 200 and 2000 ppm groups ($p<0.01$). The mean relative liver weights of both sexes in the 20000 ppm group and the mean absolute liver weights of the females in the 20000 ppm group were greater than those of the controls ($p<0.01$). The mean relative kidney weight of the 20000 ppm males was greater than that of the control ($p<0.01$). In the histopathological examination, cytoplasmic changes in the liver of both sexes in the 20000 ppm group was noted ((M) 0: 0/10 vs. 20000: 2/10, (F) 0: 0/10 vs. 20000: 9/10). In the kidneys of the 20000 ppm males, an increased incidence and severity of basophilic tubules was reported (0: 5/10, (5 grade 1) vs. 20000: 9/10, (9 grade 2)). Colloidal alteration of the thyroid was noted for both sexes in the 20000 ppm group ((M) 0: 2/10 vs. 20000: 9/10, (F) 0: 0/10 vs. 20000: 10/10). Increased thymic histiocytosis was evident for both sexes in the 20000 ppm group ((M) 0: 2/10 vs. 20000: 5/10, (F) 0: 1/10 vs. 20000: 4/10). **No adverse effect indicated**. **4-Week Dietary Toxicity NOEL:** 2000 ppm ((M) 159.2 mg/kg/day, (F) 230.6 mg/kg/day) (based upon the lesions noted in various tissues of both sexes in the 20000 ppm group). **Study supplemental** (non-guideline study). (Moore, 12/14/06)

METABOLISM STUDIES

Metabolism, Rat

53014-0149; 230030; "[^{14}C] AE-C638206: Preliminary Toxicokinetic Studies in the Rat"; (R. D'Souza; Aventis CropScience UK Limited, Toxicology, Chesterford Park, Saffron, Walden, Essex, CB10 1XL, England; Study No. TOX 99217; 11/8/00); One or two Sprague Dawley rats/sex/group were dosed with 25 or 500 mg/kg of [^{14}C] AE-C638206-benzene (batch no. 902AE-1, specific activity: 144uCi/mg, radiochemical purity: >99%) or 25 mg/kg of [^{14}C] AE-C638206-pyridine (batch no. 903AE-1, specific activity: 159 uCi/mg, radiochemical purity: >99%) orally by gavage. Unlabeled AE-C638206 (batch no. CDB234167-2, purity: 99.5%) was used to adjust the specific activity of the dosing preparations. The position of radiolabeling on the molecule or the sex of the animal did not particularly affect the recovery profile of the radiolabel. The primary route of excretion of the radiolabeled material was in the feces (76 to 85% of the administered dose at 25 mg/kg, approximately 89% of the administered dose at 500 mg/kg). Eight to 12% of the radiolabel was recovered from the urine at 25 mg/kg and 5 to 6% in the 500 mg/kg treatment group. Radiolabeled carbon dioxide represented between 0.01 and 0.06% of the administered dose. Less than 0.4% of the administered dose was recovered from the tissues at 7 days post-dose. The liver and kidneys had the highest concentrations of radiolabel. The pharmacokinetic parameters were calculated for the two 25 mg/kg treatment groups. The T_{max} values ranged from 6 to 12 hours post-dose with the maximal blood concentrations ranging from 0.95 to 2.03 ug/g of blood. Clearance from the blood ranged from 9 to 11.5 g/min. Analysis of the metabolites in the urine and feces revealed cleavage of the amide linkage and the presence of glycine, sulfate, methylmercaptan and glucuronide conjugates. The percentage of each metabolite recovered was not quantified. **Study supplemental.** (Moore, 3/1/07)

53014-0149; 230031; "[Phenyl-U-^{14}C] AE-C638206 and [Pyridyl-2,6-^{14}C] AE-C638206: Rat Blood and Plasma Kinetics Study; (P. Fisher, K. Vinck; Bayer CropScience, BP 153, F06903 Sophia Antipolis, France; Study No. SA 02012; 9/25/03); Four Sprague-Dawley CD rats/sex/group were dosed orally by gavage with 10 or 100 mg/kg of either [Phenyl-U-^{14}C] AE-C638206 (batch no. CFQ12747, radiopurity: 99.1%, specific activity: 58.05 mCi/mmole) or [Pyridyl-2,6-^{14}C] AE-C638206 (batch no. 903AE-3, radiopurity: >99%, specific activity: 62 mCi/mmole). Blood samples were recovered from the tail vein at 0.5, 1, 2, 3, 4, 6, 8, 24, and then at 24 hour intervals up to 168 hours post-dose. The radioactivity in the whole blood and plasma was determined for each of the samples and pharmacokinetic parameters were calculated. The position of the radiolabel on the molecule and the sex of the animal did not affect the pharmacokinetic parameters. The C_{max} values ranged from 1.18 to 1.50 ug equi./g in the blood and 1.59 to 2.20 ug equi./g in the plasma for the 10 mg/kg treatment and from 5.10 to 7.05 ug equi./g in the blood and from 6.67 to 9.63 ug equi./g in the plasma for the 100 mg/kg treatment. The T_{max} values ranged from 5.5 to 7.5 hours in the blood and from 6.5 to 8.0 hours in the plasma for the 10 mg/kg treatment and from 8.0 to 20 hours in both the blood and plasma for the 100 mg/kg treatment. The data indicated that absorption of the radiolabeled test material into the blood was less at the higher treatment level based on the lower proportional increase in the blood when compared to the 10:1 increase in treatment levels. **Study supplemental.** (Moore, 2/27/07)

53014-0150; 230032; "[Phenyl-U-^{14}C] AE-C638206 Rat Tissue Kinetic Study"; (P.J. Fisher; Bayer CropScience, BP 153, F06903 Sophia Antipolis, France; Study No. SA 02094; 9/12/03); Four Sprague-Dawley rats/sex/group were dosed orally by gavage with 10 or 100 mg/kg of [Phenyl-U-^{14}C] AE-C638206 (batch no. CFQ12747, radiopurity: 99.1%, specific activity: 58.05 mCi/mmole). In the 10 mg/kg treatment group, 4 animals/sex were euthanized at 8 hours, 4 males at 24 hours, 4 females at 30 hours, 4 males at 36 hours, 4 females at 48 hours, 4 males at 72 hours, and 4 females at 120 hours. At the 100 mg/kg treatment level, 4 animals/sex were euthanized at 8 hours, 4 males at 24 hours, 4 females at 30 hours, 4 animals/sex at 48 hours, 4 males at 72 hours, and 4 females at 120 hours. Specified tissues and organs were recovered and the radioactivity in those tissues and organs was determined. Extracts of liver were analyzed by HPLC-mass spectroscopy in order to identify metabolites. Peak tissue levels were observed at 8 hours post-dose for both treatment levels. No sexual difference in the distribution of the radiolabel among the tissues was apparent. The adrenal, liver and kidneys were the three organs with the highest concentration of radiolabel over the course of the study. The concentration of radiolabel in fat was initially higher than these other tissues, but diminished more rapidly. The

concentration of radiolabel in the intestinal tract demonstrated the progressive movement of the test material through the digestive tract. The percentage of administered dose absorbed into the tissues was proportionately less at the higher dose level. The concentration of radiolabel in the various tissues at 168 hours post-dose had decreased to less than 5% of the level observed at 8 hours post-dose. A total of 13 moieties were isolated from the liver extracts and represented between <0.01% and 0.20% of the administered dose. Hydroxylation and sulfation of the benzyl ring were identified as metabolic pathways. **Study supplemental.** (Moore, 3/2/07)

53014-0150; 230033; "[Phenyl-U-^{14}C] AE-C638206: Single High and Low Dose Rat A.D.E. Study"; (M. Totis; Aventis CropScience, BP 153, F06903 Sophia Antipolis, France; Study No. SA 00398; 7/20/01); Four Sprague-Dawley rats/sex/group were dosed orally by gavage with 9.61 or 76.5 mg/kg of Phenyl-U-^{14}C] AE-C638206 (batch no. 901CU-2, radiopurity: >98.3%, specific activity: 59.5 mCi/mmole). Unlabeled AE-C638206 (batch no. R001737, purity: 99.3%) was used to adjust the specific activity of the dosing preparations. Urine and feces were collected up to 7 days post-dose. The residual radioactivity in the tissues was measured at the time the animals were euthanized. The feces were the primary path of excretion with 82 to 83% of the administered dose recovered in the feces at the lower dose and 87 to 88% at the higher dose. The recovery in the urine was 10 to 13% and 5 to 7% of the administered dose, respectively. At the lower dose, 85 and 94% of the administered dose was excreted within the first 48 hours post-dose by the males and females, respectively. At the higher dose, 90 and 93% of the administered dose was excreted within the first 48 hours by the males and females, respectively. The adrenal, liver and kidneys were the three organs with the highest concentration of radiolabel. **Study supplemental.** (Moore, 3/5/07)

53014-0150; 230034; "[Phenyl-U-^{14}C] AE-C638206: Rat Metabolism Following Administration of a Single Oral Low Dose (including Amendment No. 1)"; P.J. Fisher; Aventis CropScience, BP 153, F06903 Sophia Antipolis, France; Study No. SA 00581; 3/23/04, amended, 12/8/04); Urine and fecal samples which were derived from a previous study (study no. SA 00398, rec. no. 230033) were analyzed by HPLC. The animals had been dosed orally with 9.61 mg/kg of Phenyl-U-^{14}C] AE-C638206 (batch no. 901CU-2, radiopurity: >98.3%, specific activity: 59.5 mCi/mmole). The resulting isolates were compared to known standards and subjected to liquid chromatography:mass spectroscopy in order identify their chemical structure. Over the time period for which the fecal samples were collected, structures were assigned to 82% and 81% of the recovered radioactive moieties for the males and females, respectively. This constituted 71.9 and 64.6% of the total administered dose. In the urine, structures were assigned to 52.4% and 80.3% of the radioactive isolates for the males and females, respectively. The percentage of the administered dose which was recovered in the urine samples was 9.5% and 12.7% for the males and females, respectively. Among the identified metabolites, hydroxylation of the phenyl ring alone or in conjunction with sulfation and/or the presence of methyl sulphide adducts were the predominant alterations which were observed. Glucuronide moieties associated with the hydroxylated phenyl ring were also isolated. The percentage of the administered dose which was recovered as the parent compound in the feces was 39.6 and 40.9% for the males and females, respectively. **Supplemental study.** (Moore, 3/6/07)

53014-0151; 230035; "[Phenyl-U-^{14}C] AE-C638206: Rat Metabolism Following Administration of a Single Oral High Dose (including Amendment No. 1)"; (P.J. Fisher; Aventis CropScience, BP 153, F06903 Sophia Antipolis, France; Study No. SA 01157; 2/20/04, amended, 12/8/04); Urine and fecal samples which were derived from a previous study (study no. SA 00398, rec. no. 230033) were analyzed by HPLC. The animals had been dosed orally with 76.5 mg/kg of Phenyl-U-^{14}C] AE-C638206 (batch no. 901CU-2, radiopurity: >98.3%, specific activity: 59.5 mCi/mmole). The resulting isolates were compared to known standards and subjected to liquid chromatography:mass spectroscopy in order identify their chemical structure. Over the time period for which the fecal samples were collected, structures were assigned to 99.5% and 99.0% of the recovered radioactive moieties for the males and females, respectively. This constituted 85.8% and 87.3% of the total administered dose. In the urine, structures were assigned to 40.8% and 77.0% of the radioactive isolates for the males and females, respectively. The percentage of the administered dose which was recovered in the urine samples was 4.4% and 5.7% for the

males and females, respectively. Among the identified metabolites, hydroxylation of the phenyl ring alone or in conjunction with sulfation and/or the presence of methyl sulphide adducts were the predominant alterations which were observed. Glucuronide moieties associated with the hydroxylated phenyl ring were also isolated. The percentage of the administered dose which was recovered as the parent compound in the feces was 80.0 and 81.6% for the males and females, respectively. **Supplemental study.** (Moore, 3/7/07)

53014-0151; 230036; "[Phenyl-U-^{14}C] AE-C638206: Repeat Oral Low Dose A.D.M.E. Study in the Rat (including Amendment No. 1); (P.J. Fisher; Bayer CropScience, BP 153, F06903 Sophia Antipolis, France; Study No. SA 01288; 4/9/04, amended, 12/10/04); Five Sprague-Dawley rats/sex were dosed orally daily by gavage with a dose of 9.73 mg/kg/day of [Phenyl-U-^{14}C] AE-C638206 (batch no. 901CU-2, radiopurity: >98.3%, specific activity: 59.5 mCi/mmole) for 14 days. Unlabeled AE-C638206 (batch no. R001737, purity: 99.3%) was used to adjust the specific activity of the dosing preparations. Urine, feces and cage washing were collected daily during the dosing regimen and for 6 days post-final dose. At this time, the animals were euthanized and the tissues were assayed for the presence of radiolabel compound. Urine and feces samples collected at various time points during the dosing regimen were pooled and metabolites of the parent compound were isolated and identified. The primary pathway of excretion was via the feces. For the males and females, 79 and 72%, respectively, of the administered dose was recovered in the feces. Another 15 and 21%, respectively, of the administered dose was recovered in the urine. At 6 days post-final dose, less than 0.5% of the total administered dose was recovered from the tissues. At that time, the liver, kidneys and cardiac blood had the highest concentrations of radiolabel. Among the identified metabolites, hydroxylation of the phenyl ring alone or in conjunction with sulfation were the predominant alterations which were observed. The presence of methyl sulphide adducts alone or bound with glycine were noted on the phenyl ring as well. Glucuronide moieties associated with the hydroxylated phenyl ring were also isolated. The percentage of the administered dose which was recovered as the parent compound in the feces for the time period of sample collection constituted 43.4 and 54.9% for the males and females, respectively. **Study supplemental.** (Moore, 3/8/07)

53014-0151; 230037; "[Phenyl-U-^{14}C] AE-C638206: Rat Bile Excretion Study"; (M. Totis; Aventis CropScience, BP 153, F06903 Sophia Antipolis, France; Study No. 01383; March 20, 2002); Five bile duct-cannulated Sprague-Dawley rats/sex/group were dosed orally by gavage with 9.11 or 103.2 mg/kg of Phenyl-U-^{14}C] AE-C638206 (batch no. CFQ12747, radiopurity: 99.1%, specific activity: 58.05 mCi/mmole). Non-labeled AE-C638206 (batch no. R001737, purity: 99.3%) was used to adjust the specific activities of the dosing preparations. In the low dose group, 70 and 74% of the administered dose was recovered in the bile of the males and females, respectively, during the first 48 hours post-dose. For the high dose group, the percentage of the administered dose which was recovered in the bile declined to 31 and 32% for the males and females, respectively. Five to 7 percent of the administered dose was recovered in the urine of the low dose animals. For the high dose animals, 1 to 6% of the administered dose was recovered in the urine. Recovery in the feces ranged from 21 and 19% for the males and females, respectively, in the low dose group. This recovery increased to 59 and 56% for the males and females in the high dose group. Absorption of the test material was 77 and 83% for the males and females, respectively, in the low dose group and 34 and 41%, respectively, in the high dose group. The primary site (s) of recovery in the tissues of the low and high dose groups, respectively, were the carcass and the intestinal tract content. **Study supplemental.** (Moore, 3/9/07)

53014-0151; 230038; "[2,6-Pyridyl-^{14}C] AE-C638206: Rat Tissue Kinetic Study; (P.J. Fisher; Bayer CropScience, BP 153, F06903 Sophia Antipolis, France; Study No. 02370; 9/25/03); Sixteen Sprague rats/sex were dosed orally by gavage with 10.2 mg/kg of [2,6-Pyridyl-^{14}C] AE-C638206 (batch no. GAR2034/4, radiopurity: 97%, specific activity: 70.61 mCi/mmole). Non-labeled AE-C638206 (batch no. R001737, purity: 99.3%) was used to adjust the specific activity of the dosing preparation. Four females were euthanized at 6 hours post-dose, 4 males at 7 hours, 4 animals/sex at 24 and 36 hours, 4 males at 48 hours and 4 females at 120 hours. At each time point, appropriate tissue were recovered and analyzed for radioactive content. The adrenal, liver

and kidneys were the three organs with the highest concentration of radiolabel over the course of the study. The concentration of radiolabel in fat was initially higher than these other tissues, but diminished more rapidly. The concentration of radiolabel in the intestinal tract demonstrated the progressive movement of the test material through the digestive tract. **Study supplemental.** (Moore, 3/12/07)

53014-0152; 230039; " [2,6-Pyridyl-^{14}C] AE-C638206: Single Oral Low Dose Rat A.D.E. Study (Amended)"; (R. Le Lain; Aventis CropScience, BP 153, F06903 Sophia Antipolis, France; Study No. SA 00477; 3/7/01 (amended, 3/8/01)); Four Sprague-Dawley rats/sex were dosed orally by gavage with 9.95 mg/kg of [2,6-Pyridyl-^{14}C] AE-C638206 (acyl picolide) (batch no. 903-AE-3, radiopurity: >99%, specific activity: 62.0 mCi/mmole). Non-labeled AE-C638206 (batch no. R001737, purity: 99.3%) was used to adjust the specific activity of the dosing preparation. Urine, feces and cage wash samples were collected at specified time intervals up to 7 days post-dose. At that time, the animals were euthanized and the tissues were assayed for the presence of radiolabel compound. The primary pathway of excretion was via the feces. For the males and females, 72 and 69%, respectively, of the administered dose was recovered in the feces. Another 19 and 21%, respectively, of the administered dose was recovered in the urine. At 7 days post-final dose, less than 1% of the total administered dose was recovered from the tissues. At that time, the liver, kidneys and cardiac blood as well as the intestinal contents of the males had the highest concentrations of radiolabel. **Study supplemental.** (Moore, 3/12/07)

53014-0152; 230040; "[2,6-Pyridyl-^{14}C] AE-C638206: Rat Metabolism Following Administration of a Single Oral Low Dose (including Amendment No. 1)"; (P.J. Fisher; Bayer CropScience, BP 153, F06903 Sophia Antipolis, France; Study No. SA 00550; 2/4/04 (amended, 12/10/04)); Urine and fecal samples which were derived from a previous study (study no. SA 00477, rec. no. 230039) were analyzed by HPLC. The animals had been dosed orally with 9.95 mg/kg of 2,6-Pyridyl-^{14}C] AE-C638206 (acyl picolide) (batch no. 903-AE-3, radiopurity: >99%, specific activity: 62.0 mCi/mmole). The resulting isolates were compared to known standards and subjected to liquid chromatography:mass spectroscopy in order identify their chemical structure. Over the time period for which the analyzed fecal samples were collected, structures were assigned to 72% and 78% of the recovered radioactive moieties for the males and females, respectively. The percentage of the administered dose which was recovered in the fecal samples was 67.1% and 66.6% for the males and females, respectively for this time period. In the urine, structures were assigned to 93% and 83% of the radioactive isolates for the males and females, respectively. The percentage of the administered dose which was recovered in the urine samples was 17.4% and 20.7% for the males and females, respectively, for this time period. Among the identified metabolites, hydroxylation of the phenyl ring alone or in conjunction with sulfation and/or the presence of methyl sulphide adducts were the predominant alterations which were observed. Glucuronide moieties associated with the hydroxylated phenyl ring were also isolated. The percentage of the administered dose which was recovered as the parent compound in the feces was 8.4 and 13.7% for the males and females, respectively. **Supplemental study.** (Moore, 3/12/07)

53014-0152; 230041; "[2,6-Pyridyl-^{14}C] AE-C638206: Single Oral Low Dose Rat Bile Excretion Study"; (L. Gutierrez; Bayer CropScience, BP 153, F06903 Sophia Antipolis, France; Study No. SA 02157; 2/13/03); Four bile duct-cannulated Sprague-Dawley rats/sex were dosed orally by gavage with 10.6 mg/kg of [2,6-Pyridyl-^{14}C] AE-C638206 (batch no. 903AE-3, radiopurity: >99%, specific activity: 62 mCi/mmole). Non-labeled AE-C638206 (batch no. R001737, purity: 99.3%) was used to adjust the specific activities of the dosing preparations. Fifty two percent of the administered dose was recovered in the bile of the males and females, respectively, during the first 48 hours post-dose. Five to 10 percent of the administered dose was recovered in the urine. Recovery in the feces was 40 and 39% for the males and females, respectively. Absorption of the test material was 60 and 65% for the males and females, respectively. The primary sites of recovery in the tissues was the carcass and the intestinal tract content. **Study supplemental.** (Moore, 3/13/07)

METABOLITES AND ANALOGUES

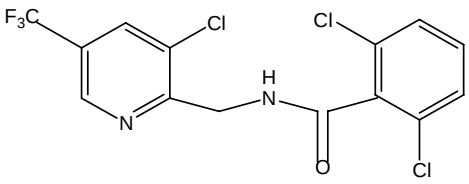
53014-0110; 226226; "Phenyl-U-^{14}C] AE C653711 (BAM): Single Oral High Dose A.D.M.E. Study in the Rat"; (L. Gutierrez; Bayer CropScience, Sophia Antipolis, F-06903, France; Project ID. SA 02327; 7/29/03); Four Sprague-Dawley rats/sex were dose orally by gavage with 150 mg/kg of Phenyl-U-^{14}C] AE C653711 (batch no. SEL/1059, specific activity: 60.9 mCi/mmole, radiochemical purity: >98%). Unlabeled AE C653711 (batch no. R001724, purity: 97.0%) was used to adjust the specific activity of the dosing preparation. Urine and feces were collected up to 168 hours post-dose. The excretion of the radiolabeled compounds was primarily via the urine (69 and 78% of the administered dose for the males and females, respectively). Another 9 and 6% of the dose was recovered in the cage wash for the two sexes, respectively. Recovery in the tissues 7 days after dosing amounted to little more than 1% of the administered dose with the radioactivity distributed amongst the tissues. Seven to 8% and 17 to 18% of the parent compound was recovered in the urine of the males and females, respectively. Otherwise, the urinary metabolites which were identified were primarily cysteine, glucuronide and sulfate conjugates. Unmetabolized parent compound was the primary radiolabeled moiety recovered in the feces. **Supplemental study.** (Moore, 1/10/07)

53014-0111; 226227; "[Phenyl-U-^{14}C] AE C653711 (BAM): Single Oral Low Dose A.D.M.E. Study in the Rat"; (L. Gutierrez; Bayer CropScience, Sophia Antipolis, F-06903, France; Project ID SA02156; 7/29/03); Four Sprague-Dawley rats/sex were dose orally by gavage with 10 mg/kg of Phenyl-U-^{14}C] AE C653711 (batch no. SEL/1059, specific activity: 60.9 mCi/mmole, radiochemical purity: >98%). Unlabeled AE C653711 (batch no. R001724, purity: 97.0%) was used to adjust the specific activity of the dosing preparation. Urine and feces were collected up to 144 hours post-dose. Exhaled carbon dioxide was collected up to 48 hours post-dose. The excretion of the radiolabeled compounds was primarily via the urine (66 and 71% of the administered dose for the males and females, respectively). Another 14 and 13% of the dose was recovered in the cage wash for the two sexes, respectively. No radioactivity was recovered in the expired air. Recovery in the tissues 6 days after dosing approximated 2% of the administered dose with the radioactivity distributed amongst the tissues. Ten to 11% of the parent compound was recovered in the urine. Otherwise, the urinary metabolites which were identified were primarily cysteine, glucuronide and sulfate conjugates. Unmetabolized parent compound was the primary radiolabeled moiety recovered in the feces. **Supplemental study.** (Moore, 1/10/07)

53014-0112; 226228; "[Phenyl-U-^{14}C] AE C653711: Repeat Oral Low Dose A.D.M.E. Study in the Rat"; (L. Guiterrez; Bayer CropScience, Sophia Antipolis, F-06903, France; Project ID. SA 03018; 8/25/03); Five Sprague-Dawley rats/sex were dose orally by gavage with 10 mg/kg/day of Phenyl-U-^{14}C] AE C653711 (batch no. SEL/1059, specific activity: 60.9 mCi/mmole, radiochemical purity: >98%) for 14 days. Unlabeled AE C653711 (batch no. R001724, purity: 97.0%) was used to adjust the specific activity of the dosing preparation. Urine and feces were collected every 24 hours during the dosing period and at 24 hour intervals up to 144 hours post-final dose. The cumulative excretion of the radiolabeled compounds was primarily via the urine (53 and 69% of the administered dose for the males and females, respectively, by day 19 of the study). Another 23 and 14% of the dose was recovered in the cage wash for the two sexes, respectively. Recovery in the tissues 6 days post-final dose approximated 1% of the administered dose with the most radioactivity recovered on the skin and fur. The parent compound comprised 9 to 12% of the cumulative dose in the urine as of day 14. Otherwise, the urinary metabolites which were identified were primarily mercapturic acid, cysteine, glucuronide and sulfate conjugates. Unmetabolized parent compound was the primary radiolabeled moiety recovered in the feces. **Supplemental study.** (Moore, 1/11/07)

53014-0113; 226229; "[Pyridyl-2,6-^{14}C] AE C657188 (PCA): Single Oral Low Dose Rat A.D.M.E. Study"; (L. Guiterrez; Bayer CropScience, Sophia Antipolis, F-06903, France; Project ID. SA 01093; 6/10/02); Four Sprague-Dawley rats/sex were dose orally by gavage with 10 mg/kg of [Pyridyl-2,6-^{14}C] AE C657188 (batch no. DCR25/1, specific activity: 36.0 mCi/mmole, radiochemical purity: 99%). AE C657188 (batch no. RAW244055/1, purity: 97.2%) was used to

adjust the specific activity of the dosing preparation. Urine and feces were collected up to 120 hours post-dose. The excretion of the radiolabeled compounds was primarily via the urine (80 and 76% of the administered dose for the males and females, respectively). Another 6 and 10% of the dose was recovered in the cage wash for the two sexes, respectively. Recovery in the tissues 5 days after dosing approximated 0.2 to 0.3% of the administered dose. Ninety eight percent of the radioactivity recovered in the urine and feces was identified as the parent compound. **Supplemental study.** (Moore, 1/12/07)



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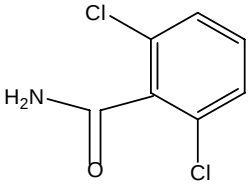

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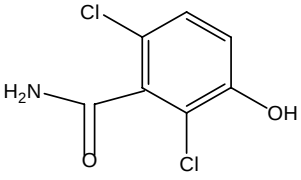

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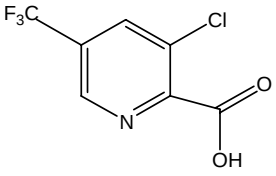

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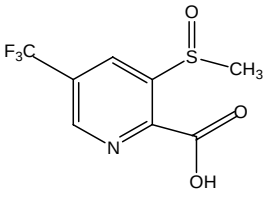

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