

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Mesosulfuron-Methyl

Chemical Code # 5898, Tolerance # 52970
SB 950 # NA

10/29/04

I. DATA GAP STATUS

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

Toxicology one-liners are attached.

All record numbers through 211265 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

indicates a study on file but not yet reviewed.

File name: T041029

Revised by T. Moore, 10/29/04

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

COMBINED, RAT

** 0071; 211247; "Rat Combined Dietary Chronic (12 and 24 Months) and Oncogenicity Study"; (A. Seeberger; Aventis Pharma Deutschland GmbH, Drug Innovation & Approval, Lead Optimization, Drug Safety Evaluation, D-65926 Frankfurt am Main, Germany; Report No. C009379; 8/14/00); Eighty Hoe:WISK(SPF 71) rats/sex/group received 0, 160, 1600 or 16000 ppm of AE F130060 technical (code. no. AE F130060 00 1C95 0001, batch no. 35316, purity: 94.6%) in the diet for up to 24 months ((M) 0, 7.46, 73.8, 764.0 mg/kg/day, (F) 0, 9.39, 94.7, 952.3 mg/kg/day). Three studies were essentially performed: (1) 12-month chronic toxicity (Study 1), 10 animals/sex/group; (2) 24-month chronic toxicity study (Study 2), 20 animals/sex/group; (3) 24-month carcinogenicity study (Study 3), 50 animals/sex/group. Survival of the animals was not affected by the treatment. There was no treatment-related effect on the mean body weights or food consumption. No treatment-related effect on food consumption was noted. No treatment-related effect was evident in the urinalysis or ophthalmology examination. Although values for the treated groups in the hematology or clinical chemistry evaluations for individual parameters were statistically different from those of the control group at various time points during the study, there was no apparent effect of toxicological significance. Although the mean absolute and/or relative weights of some organs for the treated groups were statistically different from those of the control group, there was no consistent effect for which a treatment-related effect could be identified. There were no treatment-related lesions apparent in the histopathological evaluation. **No adverse effect indicated. Chronic NOEL:** (M/F) 16000 ppm ((M) 764.0 mg/kg/day, (F) 952.3 mg/kg/day) (based upon the lack of treatment-related effects in the 16000 ppm group); **No carcinogenicity evident. Study acceptable.** (Moore, 7/20/04)

CHRONIC TOXICITY, RAT

See Combined Rat.

CHRONIC TOXICITY, DOG

** 0070; 211246; "AE F130060; Dog 12 Month Dietary Toxicity Study"; (B.A. Mallyon; Aventis CropScience UK Limited, Toxicology, Essex CB10 1XL, England; Report No. C009410; 8/30/00); Six beagle dogs/sex/group received 0, 400, 4000 or 16000 ppm of AE F130060 technical (Code no. AE F130060 00 1C95 0001, purity: 95.3% (2/24/98), 95.75 (1/25/99)) in the diet for 12 months ((M) 0, 14.7, 155, 574 mg/kg/day, (F) 0, 15.3, 169, 646 mg/kg/day). One control female was euthanized *in extremis* during week 48. She appeared to be suffering from peritonitis. No treatment-related clinical signs were evident throughout the study. Mean body weights and food consumption for the treated animals were comparable to those of the control animals. Although some of the hematology and clinical chemistry values for the treated animals were statistically different from those of the control, these differences did not represent a treatment-related effect. No treatment-related effect was evident in the ophthalmology or urinalysis. In the necropsy examination, no treatment-related effect was evident upon the mean absolute or relative organ weights. Histological examination of the 16000 ppm males revealed the incidence of minimally to slightly increased foveolar mucous secretion in the cardiac and fundus sections of the stomach (0:0/6 vs. 16000: 3/6). One of these 3 animals also suffered from chronic superficial gastritis. One of the six control females also had this finding. **No adverse effect indicated. Chronic NOEL:** (M) 4000 ppm (155 mg/kg/day) (based upon the incidence of increased foveolar mucous secretion in the stomach of the 16000 ppm males) (F) 16000 ppm (646 mg/kg/day) (based upon the lack of a treatment-related effect at the highest dose tested). **Study acceptable.** (Moore, 7/26/04)

ONCOGENICITY, RAT

See Combined Rat.

ONCOGENICITY, MOUSE

** 0072; 211248; "Mouse Dietary Oncogenicity (18 Months) Study"; (A. Seeberger; Aventis Pharma Deutschland GmbH, Drug Innovation & Approval, Lead Optimization, Drug Safety Evaluation, D65926 Frankfurt am Main, Germany; Report No. C009460; 8/17/00); Sixty CD-1 mice/sex/group received 0, 80, 800 or 8000 ppm of AE F130060 Technical (code no. AE F130060 00 1C95 0001; batch no. Pfl 35316; purity: 94.6% (4/3/97), 95.3% (3/3/98)) in the diet for 18 months ((M) 0, 10.6, 102.8, 1069 mg/kg/day, (F) 0, 13.9, 129.8, 1356 mg/kg/day). There was no apparent treatment-related effect upon the survival of the animals. The mean body weights for both sexes in the 8000 ppm group were lower than those of the controls at various times during the study. No treatment-related effect upon food consumption was evident. Although the values for some of the hematology and clinical chemistry parameters of the treated animals were statistically different from those of the controls, the differences were not apparently related to treatment (note: a significant increase in the white blood cell count was noted for both sexes in the 8000 ppm group after 18 months without any apparent toxicological consequences). In the necropsy examination, the absolute and/or relative weights for some of the organs were statistically different from those of the controls. These differences were not apparently treatment-related. In the histopathological examination, the incidence of neoplastic or non-neoplastic lesions did not demonstrate a possible treatment-related effect. **No adverse effect indicated. Chronic NOEL:** (M/F) 800 ppm ((M) 102.8 mg/kg/day, (F) 129.8 mg/kg/day) (based on the lower mean body weights of the 8000 ppm animals); **no carcinogenicity was evident. Study acceptable.** (Moore, 7/26/04)

REPRODUCTION, RAT

** 0075; 211251; "Rat Two-Generation Feeding-Reproduction Toxicity Study with AE F130060 - Substance Technical (Code: AE F130060 00 1C95 0001)"; (G. Horstmann; Aventis Pharma Deutschland GmbH, ProTox, D-65795 Hattersheim, Germany; Report no. C010081; 10/10/00); Twenty five Sprague-Dawley rats/sex/group received 0, 160, 1600 or 16000 ppm of AE F130060 Technical (code no. AE F130060 001C95 0001, batch no. Pfl. 35316, purity: 94.6%, retested 95.3% (2/24/98), 95.7% (1/18/99)) in the diet for two generations. The treatment period for the P parents included 10 weeks prior to mating, the mating period (litter F1a), 3 weeks both for gestation and lactation, a second pre-mating period of 2 weeks, the mating (litter F1b), 3 weeks both for gestation and lactation. At that time, 25 F1 animals/sex/group were selected as parents and treated for 10 weeks in the pre-mating period, the mating period (litter F2a), and 3 weeks both for gestation and lactation, followed by a second pre-mating period of 1 week, the mating period (litter F2b), and 3 weeks of both gestation and lactation. There were no apparent treatment-related deaths during the study. There was no treatment-related effect on mean body weights or food consumption throughout the study. There was no treatment-related effect upon organ weights for either parental generations or the F2b weanlings. The histopathological examination did not reveal any treatment-related lesions in the reproductive organs. There were no treatment-related effects upon the reproductive parameters. The pup viability and mean pup weights were not affected by the treatment during the lactation periods. **No possible adverse effect evident. Parental NOEL:** 16000 ppm (based upon the lack of treatment-related effects in the 16000 ppm group) ((M) 840.4 to 2881.7 mg/kg/day, (F) 1159.4 to 3670.7 mg/kg/day), **Reproductive NOEL:** 16000 ppm (based upon the lack of treatment-related effects on the dams in the 16000 ppm group) ((F) 1159.4 to 3670.7 mg/kg/day), **Developmental NOEL:** 16000 ppm (based upon the lack of treatment-related effects on the pups in the 16000 ppm group) ((F): 1159.4 to 3670.7 mg/kg/day); **Study acceptable.** (Moore, 8/2/04)

TERATOLOGY, RAT

** 0074; 211250; "AE F130060; Substance Technical; Code: AE F130060 00 1C95 0001; Rat Oral Developmental Toxicity (Teratogenicity) Study"; (Th. Hofmann; HMR Deutschland GmbH, ProTox, D-65795 Hattersheim, Germany; Report No. C003932; 5/4/99); Twenty three mated Sprague-Dawley female rats/group were dosed orally by gavage with 0, 100, 315 or 1000 mg/kg/day of AE F130060 Technical (code no. AE F130060 001C95 0001, batch no. Pfl. 35316, purity: 94.6%) from gestation day 7 through gestation day 16. No maternal deaths resulted from the treatment. There were no apparent treatment-related effects upon mean body gain or food consumption. There were no treatment-related effects upon fetal development. **No adverse effect indicated. Maternal NOEL:** 1000 mg/kg/day (based on the lack of a treatment-related effect on the 1000 mg/kg group); **Developmental NOEL:** 1000 mg/kg/day (based on the lack of a treatment-related effect on the 1000 mg/kg group). **Study acceptable.** (Moore, 7/27/04)

TERATOLOGY, RABBIT

** 0073; 211249; "AE F130060; Substance Technical; Code: AE F130060 00 1C95 0001; Rabbit Oral Developmental Toxicity (Teratogenicity) Study"; (Th. Hofmann; HMR Deutschland GmbH, Drug Innovation & Approval, Lead Optimization, Department of Toxicology/Pharmacology, D-65926 Frankfurt am Main, Germany; Report No. C000843; 8/24/98); Fifteen mated female Himalayan rabbits/group were dosed orally by gavage with 0, 100, 315 or 1000 mg/kg/day of AE F130060 Technical (code no. AE F130060 001C95 0001, batch no. Pfl. 35316, purity: 94.6%) from gestation day 6 through gestation day 18. No maternal deaths resulted from the treatment. There were no apparent treatment-related effects upon mean body gain or food consumption. There were no treatment-related effects upon fetal development. **No adverse effect indicated. Maternal NOEL:** 1000 mg/kg/day (based on the lack of a treatment-related effect on the 1000 mg/kg group); **Developmental NOEL:** 1000 mg/kg/day (based on the lack of a treatment-related effect on the 1000 mg/kg group). **Study acceptable.** (Moore, 7/27/04)

GENE MUTATION

** 0076; 211252; "Hoe 130060; Substance, Technical (Code: Hoe 130060 00 ZC96 0001) Bacterial Reverse Mutation Test"; (W. Muller; Hoechst Aktiengesellschaft, Pharma Development Corporate Toxicology, 65926 Frankfurt am Main, Germany; Report No. A56743; 4/24/96); *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° C with Hoe130060 Technical (batch no. Lor 20020 W6, purity: 95.6%) at concentrations ranging from 4 to 5000 ug/plate with and w/o activation in the first trial. In the second trial, the range of concentrations was reduced to 0.16 to 500 ug/plate for the *S. typhimurium* strains. For the *E. coli* strain WP2 uvrA strain, the exposure levels were the same as in the first trial. Each treatment level was plated in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 9/3/04)

** 0078; 211254; "AE F130060; Substance, Technical (Code: AE F130060 00 1C95 0001) *In Vitro* Chinese Hamster Lung V79 Cell HPRT Mutation Test"; (W. Muller; Hoechst Marion Roussel, Preclinical Development, Drug Safety, 65926 Frankfurt am Main, Germany; Report No. A67081; 2/12/98); Chinese Hamster lung V79 cells were treated with AE F130060 Technical (code no. AE F130060 00 1C95 0001; batch no. Pfl. 35316; purity: 94.6%) at concentrations ranging from 25 to 2500 ug/ml for 4 hours at 37° C (precipitation of the test material was noted at concentrations \geq 250 ug/ml). Two trials 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, 8/24/04)

CHROMOSOME EFFECTS

** 0077; 211253; "AE F130060; Substance, Technical (Code: AE F130060 00 1C95 0001) *In Vitro* Mammalian Chromosome Aberration Test in V79 Chinese Hamster Lung Cells"; (W. Muller; Hoechst Marion Roussel, Preclinical Development, Drug Safety, 65926 Frankfurt am Main, Germany; Report No. A67555; 5/11/98); V79 Chinese hamster lung cells were exposed to concentrations of AE F130060 Technical (code no. AE F130060 00 1C95 0001; batch no. Pfl. 35316; purity: 94.6%) ranging from 7.9 to 2500 ug/ml under conditions of activation and non-activation at 37° C. For the non-activated cultures, the cells were exposed to the test material for 20 or 28 hours. In the activated samples, the cells were exposed for 3 hours, washed and incubated for an additional 17 or 25 hours. An Arochlor 1254-induced rat liver S9 fraction was used to metabolize the test material. Two trials were performed. Duplicate cultures were performed at each treatment level. Fifty metaphases per culture/slide were evaluated (200 metaphases per treatment level). There was no treatment-related increase in chromosomal cell aberrations. Positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 8/4/04)

** 0080; 211256; "AE F130060; Substance, Technical, Code: AE F130060 00 1C95 0001: Mouse Micronucleus Test"; (W. Muller; Hoechst Marion Roussel, Preclinical Development, Drug Safety, D-65926 Frankfurt am Main, Germany; Report No. A67143; 2/3/98); Fifteen HsdWin:NMRI mice/sex/group were dosed orally by gavage with 0, 200, 1000 or 2000 mg/kg of AE F130060 Technical ((code no. AE F130060 00 1C95 0001); batch no. Pfl. 35316; purity: 94.6%). Five animals/sex/group/time point were euthanized at 12, 24 and 48 hours post-dose. A positive control group of 5 mice/sex was dosed in the same manner with 50 mg/kg of Endoxan® (cyclophosphamide). The animals were euthanized at 24 hours post-dose. The femoral bone marrow was harvested and evaluated for the presence of micronuclei in polychromatic erythrocytes (PCE). One thousand PCEs were evaluated per animal. The ratio of PCEs to normocytic erythrocytes was noted as well. There was no treatment-related increase in the number of PCE with micronuclei per 1000 PCEs. **No adverse effect indicated.** The positive control was functional. **Study acceptable.** (Moore, 8/26/04)

DNA DAMAGE

** 0079; 211255; "AE F130060; Substance, Technical; Code: AE F130060 00 1C95 0001: Detection of DNA Strand Breaks in Primary Hepatocytes of Male Rats *in Vitro*: UDS - Test in Primary Rat Hepatocytes"; (W. Muller; Hoechst Marion Roussel Deutschland GmbH, Drug Innovation and Approval, Lead Optimization, D-65926 Frankfurt am Main, Germany; Report No. A67689; 6/3/98); Primary rat hepatocyte cultures were exposed to AE F130060 Technical (code no. AE F130060 00 1C95 0001; batch no. Pfl. 35316; purity: 94.6%) at concentrations ranging from 1.0 to 2500 ug/ml for 16 to 20 hours at 37° C. Vehicle and positive (2-AAF, 1.0 ug/ml) controls were included in the assay. There were 2 trials with 2 cultures/treatment level. Fifty cells per coverslip were scored per concentration per trial. Precipitation was noted at ≥ 100 ug/ml in both trials. There was no treatment-related increase in unscheduled DNA synthesis. The positive control was functional. **No adverse effect indicated. Study acceptable.** (Moore, 8/25/04)

NEUROTOXICITY

Not required at this time.

SUBCHRONIC

Subchronic Rat Dietary Study

52970-0067; 211243; "Hoe 130060; Substance, Technical, Hoe 130060 00 ZC96 0002; Subchronic (90 Days Feeding) Oral Toxicity Study in Rats"; (R. Hammerl; Hoechst Marion Roussel Deutschland GmbH, Drug Innovation & Approval, Lead Optimization, Department of Toxicology/Pathology, D-65926 Frankfurt am Main, Germany; Report No. C004205; 5/28/99); Ten Hoe:WISK(SPF 71) rats/sex/group received 0, 240, 1200, 6000 or 12000 ppm of Hoe 130060 Technical (code no. Hoe 130060 00 ZC96 0002, batch no. M300, purity: 96.0%) for 13 weeks in the main study ((M) 0, 17.5, 88.6, 435.0, 907.5 mg/kg/day, (F) 0, 19.1, 96.1, 474.7, 976.5 mg/kg/day). Recovery groups of 10 additional animals/sex in the control and 12000 ppm groups were maintained for 4 weeks post-dosing. No deaths resulted from the treatment. There were no effects upon the mean body weights or food consumption of the treated animals. There were no apparent treatment-related effects noted in the ophthalmology, urinalysis or hematology. In the clinical chemistry evaluation, although the values for certain parameters for the treated groups were statistically different from those of the controls, these differences were not considered to be of toxicological significance. In the necropsy examination, the mean absolute and/or relative weights for some organs were statistically different from those of the control groups. However, no treatment-related lesions were evident in the histopathology examination and no target organ could be identified. **No adverse effect indicated. Subchronic NOEL:** (M/F) 12000 ppm ((M) 907.5 mg/kg/day, (F) 976.5 mg/kg/day) (based upon the lack of treatment-related effects at the highest dose tested); **Study acceptable.** (Moore, 7/16/04)

Subchronic Mouse Dietary Study

52970-0068; 211244; "Hoe 130060; Substance Technical, Hoe 130060 00 ZC96 0002; Subchronic (90 Days Feeding) Oral Toxicity Study in Mice"; (R. Hammerl; Hoechst Marion Roussel Deutschland GmbH, Drug Innovation & Approval, Lead Optimization, Department of Toxicology/Pathology, D-65926 Frankfurt am Main, Germany; Report No. C006716; 5/28/99); Ten CD1 mice/sex/group received 0, 140, 1000, or 7000 ppm of Hoe 130060 Technical (code no. Hoe 130060 00 ZC96 0002, purity: 96.0%) in the diet for 13 weeks ((M) 0, 25.5, 176.1, 1238 mg/kg/day, (F) 0, 32.3, 206.1, 1603 mg/kg/day). No animals died during the study. There was no treatment-related effect upon mean body weights or food consumption. In the hematology evaluation, the leucocyte count was reduced for the 1000 ppm males and for both sexes in the 7000 ppm group ($p < 0.05$). Although the values for various clinical chemistry parameters of the treated animals were statistically different from those of the controls, these differences were not considered to be biologically significant. In the necropsy examination, the mean absolute and relative liver weights for the 7000 ppm males were lower than those of the control ($p < 0.05$). In the histological examination, there was an increased incidence of glycogen loss in the 7000 ppm males (0: 1/10 vs. 7000: 4/10). **Possible adverse effect:** reduced leucocyte count. **Subchronic NOEL:** (M) 140 ppm (25.5 mg/kg/day) (F) 1000 ppm (206.1 mg/kg/day) (based upon reduced leucocyte counts in the 1000 ppm male group and the 7000 ppm female group). **Study acceptable.** (Moore, 7/21/04)

Subchronic Dog Dietary Study

52970-0069; 211245; "AE F130060 - Substance Technical (Code: AE F130060 00 1C95 0001) Dog Oral 90 Day Repeated Dose Toxicity Study (Dietary Administration)"; (I. Stammberger; Aventis Pharma Deutschland GmbH, Drug Innovation & Approval, Lead Optimization, Drug Safety Evaluation, D-65795 Hattersheim, Germany; Report No. C009014; 7/7/00); Six beagle dogs/sex/group received 0, 750, 3750 or 7500 ppm of AE F130060 technical (Code no. AE F130060 00 1C95 0001, purity: 94.6%) in the diet for 13 weeks ((M) 0, 63, 348, 648 mg/kg/day, (F) 0, 75, 380, 734 mg/kg/day). Doses were equivalent to 2000, 10000 or 20000 ppm of 300 g dry meal before adding 500 grams of water, 800 g/animal/day. No deaths resulted from the treatment. No treatment-related clinical signs or effects upon the mean body weights or food consumption were evident. No treatment-related effect was noted in the hematology or urinalysis evaluations. Although some of the values of the treated animals for the clinical chemistry parameters were statistically different from those of the controls, these differences were not toxicologically significant. Although mean absolute and/or relative weights for some organs among the treated

animals were statistically different from those of the controls, these differences were not of toxicological significance. No treatment-related lesions were evident in the histological examination. **No adverse effect evident. Subchronic NOEL:** (M/F) 7500 ppm ((M) 648 mg/kg/day, (F) 734 mg/kg/day) (based upon the lack of treatment-related effects in the highest dose tested); **Study acceptable.** (Moore, 7/22/04)

METABOLISM STUDIES

52970-0081; 211257; “[2-Pyrimidyl-¹⁴C] AE F130060: Rat Preliminary Toxicokinetics: Absorption, Distribution and Elimination - Oral Low Dose (10 mg/kg body weight) and Oral High Dose (1000 mg/kg body weight)”; (J. Maas, W. Vetter; HMR Preclinical Development, Pharmacokinetics, Germany, Hoechst Aktiengesellschaft, D-65926 Frankfurt am Main, Germany; Report No. C006347; 7/1/97); Two Wistar rats/sex/group were dosed orally by gavage with a nominal 10 or 1000 mg/kg of [2-Pyrimidyl-¹⁴C] AE F130060 (batch no. Z 26003-0, radiochemical purity: 96.9% (HPLC determination), specific activity: 4333 MBq/g; purity: 98.1%). Urine and feces samples were collected from each animal at 24 hour intervals through 7 days post-dose (only samples collected for the 1st 72 hours were analyzed). After 7 days, the animals were euthanized and the carcasses were subjected to whole-body autoradiography. The predominant route of excretion was in the feces. Eighty to 90% of the administered dose for the low dose group was recovered in the feces. This percentage increased to greater than 95% in the high dose group. The data were not adequate to determine the actual percentage of the dose which was absorbed because a biliary excretion study was not performed. There was no apparent difference between the sexes. Seventy five to 100% of the administered dose was excreted in the first 24 hours post-dose. The excretion half lives for the individual animals ranged between 6.0 and 8.8 hours for urinary excretion and between 3.1 and 9.3 hours for fecal excretion with no apparent difference evident for the different dosing levels. No radiolabeling was ascertained to be in the carcass after 168 hours post-dose. **Study supplemental.** (Moore, 8/26/04)

52970-0082; 211258; “Rat Preliminary Toxicokinetics: Metabolism - Oral Low Dose (10 mg/kg body weight) and Oral High Dose (1000 mg/kg body weight)”; (S. Lauck-Birkel, B. Strunk; Aventis CropScience Oekochemie, D-65926 Frankfurt am Main, Germany; Report No. C008354; 7/19/00); Two Wistar rats/sex/group were dosed orally by gavage with a nominal 10 or 1000 mg/kg of [2-Pyrimidyl-¹⁴C] AE F130060 (batch no. Z 26003-0, radiochemical purity: 96.9% (HPLC determination), specific activity: (low dose) 478.95 MBq/g, (high dose) 5.05 MB/q/g). Urine and feces samples were collected from each animal at 24 hour intervals through 7 days post-dose (only samples collected for the 1st 72 hours were analyzed) (see report no. C006347 (vol. 52970-0081, record no. 211256)). In this study, the radiolabeled compounds in the urine and feces were isolated and identified. The predominant radiolabeled material which was recovered in either the urine or the feces was the unmetabolized parent compound (75 to 87% of the administered dose for either dosing regimen. Cleavage of the sulfonylurea-bridge was one of the main pathways of metabolism (AE F092944) as noted in the fecal metabolites. Other paths of metabolism included O-demethylation on the pyrimidine (AE F160459) and cleavage of the methanesulfonamidomethyl side chain (AE F151015, AE 0195141). One metabolite (AE F118772) resulted from the combined cleavage of the sulfonylurea bridge and O-demethylation of the pyrimidine. **Study supplemental.** (Moore, 8/27/04)

52970-0083; 211259; “[Phenyl-U-¹⁴C] AE F130060: Rat - Absorption, Distribution and Elimination - Single Oral Low Dose (10 mg/kg body weight)”; (J. Maas; HMR Deutschland GmbH, DI&A; Lead Optimization, DMPK Germany, D-65926 Frankfurt am Main, Germany; Report No. C006348; 7/21/97); Wistar rats were dosed orally by gavage with 10 mg/kg of [Phenyl-U-¹⁴C] AE F130060 (batch no. Z 27038-0; specific activity: 2862 MBq/g; radiochemical purity: 99% (HPLC)) in two studies. In the first study, 4 animals/sex were dosed and urine and feces were collected periodically at specified time points up to 72 hours post-dose. In the second study, 4 animals/sex were dosed and blood samples were collected from the tail vein at specified time points up to 7 days post-dose. At 72 hours post-dose, radiolabeling in particular tissue samples was determined. The feces were the predominant route of excretion with 85 to 90% of the

administered dose being recovered via that route. Eighty-eight and 92% of the administered dose was recovered in the first 24 hours. The half-lives for urine and feces excretion were 7.8 and 5.2 hours for the males and 8.0 and 5.0 hours for the females. The maximal level of radiolabeling in the blood was achieved between 2 and 4 hours post-dose. The half-life for the elimination of radiolabeling from the blood was 12.0 and 10.6 hours for the males and females, respectively. The liver was the predominant tissue at which radioactivity was recovered at 72 hours post-dose. The percent of the administered dose which was recovered was 0.014 and 0.013% for males and females, respectively. **Supplemental study** (the study was limited to the examination of the excretion profile for one dose level and no biliary excretion or identification of metabolites was performed). (Moore, 9/3/04)

52970-0084; 211260; “[Phenyl-U-¹⁴C] AE F130060: Rat -Excretion via the Bile - Single Oral Low Dose (10 mg/kg body weight)”; (J. Maas; HMR Deutschland GmbH, DI&A; Lead Optimization, DMPK Germany, D-65926 Frankfurt am Main, Germany; Report No. C006349; 7/23/99); Four bile-duct cannulated Wistar rats/sex were dosed with 10 mg/kg of [Phenyl-U-¹⁴C] AE F130060 (batch no. Z 27063-1; specific activity: 1350 MBq/g; radiochemical purity: 99.9% (HPLC)) and bile samples were collected over specified time intervals up to 12 hours post-dose. By 12 hours post-dose, 7 to 9% of the administered dose was recovered from the bile. An additional 63 to 65% of the dose was recovered in the gastrointestinal tract at the end of the 12 hour period. A predominant fraction of the radiolabel was recovered in the small intestines. **Study supplemental** (study focused solely on the biliary secretion of the radiolabeled test material). (Moore, 9/7/04)

52970-0085; 211261; “Rat Metabolism - Single Oral Low Dose (10 mg/kg body weight)”; (S. Lauck-Birkel, B. Strunk; Aventis CropScience, Oekochemie, D65926 Frankfurt am Main, Germany; Report No. C008356; 5/15/00); Wistar rats of both sexes were dosed orally by gavage with 10 mg/kg of either [Phenyl-U-¹⁴C] AE F130060 (batch no. Z 27038-0; specific activity: 2862 MBq/g; radiochemical purity: 99% (HPLC) or [Phenyl-U-¹⁴C] AE F130060 (batch no. Z 27063-1; specific activity: 1350 MBq/g; radiochemical purity: 99.9% (HPLC)). For the animals treated with the former compound, urine and feces were collected at specified time intervals up to 72 hours post-dose (report no. C006348, vol no. 52970-0083, record no. 211259). For the animals treated with the latter compound, bile samples were collected for specified time intervals up to 12 hours post-dose (report no. C006349, vol. no. 52970-0084, rec. no. 211260). In this study, identification and quantification of the metabolites in these samples was undertaken. Pooled urine and bile samples were directly analyzed by radio-HPLC or TLC. The homogenized fecal samples were centrifuged and the supernatant water phase analyzed by HPLC. The residue was extracted using water:acetonitrile (1:4) and the samples were concentrated by rotary evaporation and analyzed by HPLC or TLC. Structures of particular metabolites were confirmed by HPLC/MS/MS. Ninety to 95% of the administered dose was recovered as the parent compound. The metabolic pathways included the cleavage of the sulfonamide bridge, O-demethylation of the pyrimidine ring and cleavage of the methanesulfon-amidomethyl side chain. **Study supplemental** (only identification and quantification of metabolites were performed in this study). (Moore, 9/8/04)

52970-0086; 211262; “[Phenyl-U-¹⁴C] AE F130060: Rat - Absorption, Distribution and Elimination - Oral High Dose (1000 mg/kg body weight)”; (J. Maas, R. Braun; HMR Preclinical Development, Pharmacokinetics, Germany, Hoechst Aktiengesellschaft, D-65926 Frankfurt am Main, Germany; Report No. A67074; 1/29/98); Wistar rats were dosed orally by gavage with 1000 mg/kg of [Phenyl-U-¹⁴C] AE F130060 (batch no. Z 27019-1; specific activity: 10.78 MBq/g; radiochemical purity:> 99% (HPLC)) in two studies. In the first study, 4 animals/sex were dosed and urine and feces were collected periodically at specified time points up to 72 hours post-dose. In the second study, 4 animals/sex were dosed and blood samples were collected from the tail vein at specified time points up to 7 days post-dose. At 72 hours post-dose, radiolabeling in particular tissue samples was determined. The feces were the predominant route of excretion with 98 to 99% of the administered dose being recovered via that route. Eighty-eight and 96% of the administered dose was recovered in the first 24 hours from the females and males, respectively. The half-lives for urine and feces excretion were 7.1 and 3.8 hours for the males and

9.9 and 3.7 hours for the females. The maximal level of radiolabeling in the blood was achieved between 2 and 4 hours post-dose. The half-life for the elimination of radiolabeling from the blood was 11.5 and 8.2 hours for the males and females, respectively. The liver was the only tissue from which radioactivity was recovered at 72 hours post-dose. The percent of the administered dose which was recovered was 0.001% for males. In the females, radioactivity was recovered from the liver of only one animal, at a level of 0.001%. Radioactivity was recovered from the blood of two males at a level of 0.001%. **Supplemental study** (the study was limited to the examination of the excretion profile for one dose level and no biliary excretion or identification of metabolites was performed). (Moore, 9/13/04)

52970-0087; 211263; "Rat Metabolism - Single Oral High Dose (1000 mg/kg body weight)"; (S. Lauck-Birkel, B. Strunk; Aventis CropScience, Oekochemie, D65926 Frankfurt am Main, Germany; Report No. C008355; 8/3/00); Wistar rats of both sexes were dosed orally by gavage with 1000 mg/kg of [Phenyl-U-¹⁴C] AE F130060 (batch no. Z 27019-1; specific activity: 10.78 MBq/g; radiochemical purity:> 99% (HPLC)). Urine and feces were collected at specified time intervals up to 72 hours post-dose (report no. A67074, vol no. 52970-0086, record no. 211262). In this study, identification and quantification of the metabolites in these samples was undertaken. Pooled urine and bile samples were directly analyzed by radio-HPLC or TLC. The homogenized fecal samples were centrifuged and the supernatant water phase analyzed by HPLC. The residue was extracted using water:acetonitrile (1:4) and the samples were concentrated by rotary evaporation and analyzed by HPLC or TLC. Structures of particular metabolites were confirmed by HPLC/MS/MS. Eighty one to 89% of the administered dose was recovered as the parent compound. The metabolic pathway included the cleavage of the sulfonylurea bridge, O-demethylation of the pyrimidine ring and cleavage of the methanesulfon-amidomethyl side chain. **Study supplemental** (only identification and quantification of metabolites were performed in this study). (Moore, 9/13/04)

52970-0088; 211264; "[Phenyl-U-¹⁴C] AE F130060; Rat - Absorption, Distribution and Elimination - Repeated Oral Dose (7 x 250 mg/kg body weight)"; (J. Maas; HMR Deutschland GmbH, DI&A, Lead Optimization, DMPK Germany, D-65926 Frankfurt am Main, Germany; Report No. C006350; 8/26/99); Eighteen Wistar rats/sex were dosed orally by gavage with 250 mg/kg of [Phenyl-U-¹⁴C] AE F130060 (batch no. Z 28008-1; specific activity: 40.33 MBq/g; radiochemical purity: >98% (HPLC)). Three animals/sex received one dose and were euthanized at 3 hours post-dose. Another 3 animals/sex received 4 daily doses and were then euthanized at 3 hours post-final dose. The remaining 12 animals/sex received 7 daily doses and 3 animals/sex/time point were euthanized at 3, 24, 48 and 168 hours post-final dose. Urine and feces were collected at specified time intervals for each group. Particular tissues were dissected from the animals in each of the groups and analyzed for the presence of radiolabeled compound. Ten to 15% of the total administered radiolabel was excreted in the feces daily during the 7 day dosing period. Recovery in the urine ranged from 0.17 to 0.33% of the total administered dose for the males and from 0.28 to 0.98% for the females during the same time period. These results indicated that a steady-state in the excretion profile had been achieved. Ninety-seven and ninety three percent of the total administered dose was recovered in the feces of the males and females, respectively, by the end of the 168 hour collection period. Two and 4.5% of the dose was recovered in the urine of the males and females, respectively. Recovery of the radiolabel in the tissues diminished perceptively as the number of daily doses increased from 1 to 4 to 7. By 168 hours post-final dose, the presence of the radiolabel in the tissues was negligible. The elimination half-lives from the blood and plasma as determined between 144 and 192 hours of the study were 13.1 and 13.3 hours for the males, respectively, and 9.9 and 9.4 hours for the females, respectively. **Study supplemental** (study only included a repeated dosing regimen and not the other parameters which are required in a guideline metabolism study). (Moore, 9/14/04)

52970-0089; 211265; "Rat Metabolism - Repeated Oral Dose (7 x 250 mg/kg body weight)"; (S. Lauck-Birkel, B. Strunk; Aventis CropScience, Oekochemie, D-65926 Frankfurt am Main, Germany; Report No. C008357; 5/15/00); In a previous study, 18 Wistar rats/sex were dosed orally by gavage with 250 mg/kg of [Phenyl-U-¹⁴C] AE F130060 (batch no. Z 28008-1; specific

activity: 40.33 MBq/g; radiochemical purity: >98% (HPLC)) (report no. C006350, vol. 52970-0088, 211264). Three animals/sex received one dose and were euthanized at 3 hours post-dose. Another 3 animals/sex received 4 daily doses and were then euthanized at 3 hours post-final dose. The remaining 12 animals/sex received 7 daily doses and 3 animals/sex/time point were euthanized at 3, 24, 48 and 168 hours post-final dose. Urine and feces were collected at specified time intervals for each group. The radiolabeled compounds recovered from pooled urine and fecal samples from some of these animals were identified and quantified by HPLC and TLC. After one dose of 250 mg/kg, 79 to 86% of the administered dose was recovered in the feces as unmetabolized parent compound up to 24 hours post-dose. Another 1 to 2% of the unmetabolized compound was recovered in the urine over this time period. After 7 doses, 95 to 99% of the radiolabeled compound which was recovered in the feces up to 48 hours post-final dose was unmetabolized parent compound. The percentage of total administered dose which was recovered in the feces over this time period was 15 to 16%. The metabolic pathways included the cleavage of the sulfonylurea bridge, O-demethylation of the pyrimidine ring and cleavage of the methanesulfon-amidomethyl side chain. **Study supplemental** (study included only an identification and quantification of radiolabeled compounds recovered in the urine and feces of study animals). (Moore, 9/15/04)