

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

FORAMSULFURON

Chemical Code # 5851, Tolerance # 52939

10 October 2003

I. DATA GAP STATUS

Combined, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	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:	Data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, possible adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

All record numbers through 203990 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

indicates a study in review.

File name: T031015

Prepared by Green, 15 October 2003

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

COMBINED, RAT

**52939-086 203986, "Rat Dietary Combined Chronic Toxicity and Oncogenicity Study", (P. Higgs, AgrEvo UK Limited, Toxicology, Chesterford Park, Saffron Walden, Essex, England, Report # TOX/99/262-42, 7 March 2000). 70 Sprague Dawley CRL:CD (IGS) BR rats per sex per group received technical grade AE F130360 (Hoe 130360) (94.6% foramsulfuron) in the diet at 0 (Modified SQC Expanded Rat and Mouse Maintenance Diet No. 1), 100, 600, 6000, and 20000 ppm for 104 weeks. An interim sacrifice (chronic phase) of 20 per sex per group at 52 weeks were performed. No treatment related effects were indicated for mortality, clinical signs, bodyweight, food consumption, clinical pathology, necropsy, or histopathology at any dose level. Chronic and oncogenicity NOEL = 20000 ppm (849 mg/kg/day for males and 1135 mg/kg/day for females). Treatment levels were sufficient to satisfy limit test requirements. No adverse effects. Acceptable. (Green and Gee, 8/6/03).

CHRONIC TOXICITY, DOG

**52939-079 203973, "Dog 12 Month Oral Toxicity Study" (P. Higgs, AgrEvo UK Limited, Chesterford Park, Saffron Walden, Essex, England, Report # TOX/99/262-37, 23 September 1999). 4 Beagle dogs per sex per group received Technical AE F130360 (96.4% foramsulfuron) by gavage at 0 (methyl cellulose in distilled water), 5, 100, and 1000 mg/kg/day for 12 months. There were not treatment related findings for clinical signs, bodyweight, food consumption, hematology, serum chemistry, necropsy, and histopathology up to 1000 mg/kg/day. No mortalities were reported. Beige feces and vomit were seen on occasion at 1000 mg/kg/day (test was a beige or cream powder). No adverse effects. Chronic NOEL = 1000 mg/kg/day. Limit test conditions were met. Acceptable. (Green and Gee, 8/6/03).

ONCOGENICITY, MOUSE

**52939-087 203987, "Mouse Dietary Oncogenicity Study", (J. Wood, Covance Laboratories Limited, North Yorkshire, England, Report # TOX/99/262-45, 16 December 1999). 51 Crl:CD-1(ICR)BR mice per sex per group received AE F130360 technical (96.4% foramsulfuron) in the diet at 0 (SQC Rat and Mouse Maintenance Diet No. 1, Expanded, Ground Fine), 40, 800, and 8000 ppm for 80 weeks. Dosing levels exceeded limit test conditions. Group mean compound consumption in mg/kg/day for weeks 1 through 80 was 1115.1 mg/kg/day for males and 1357.5 mg/kg/day for females at the high dose level. Toxicity was not indicated at any treatment level. Female survival was slightly improved at the top dose level relative to controls. Clinical signs, bodyweights, food consumption, organ weights, necropsy, and histopathology showed no signs of a treatment effect and were generally consistent with findings expected for mice of that age. Oncogenicity was not indicated. Chronic and oncogenicity NOEL = 8000 ppm. No adverse effects. Acceptable. (Green and Gee, 8/7/03).

REPRODUCTION, RAT

**52939-088 203988, "Rat Dietary Two-Generation Reproductive Toxicity Study", (Gregg D. Cappon, WIL Research Laboratories, Inc., Ashland, OH., Report # WIL-303004, 22 October

1999). 30 Sprague Dawley CrI:CD[®](SD)BR rats per sex per group per generation received AE F130360 Technical (96.1% foramsulfuron) in the diet at 0 (PMI Nutrition International Inc., Certified Rodent LabDiet[®] 5002), 100, 1225, and 15000 ppm through 2 generations (one litter per generation). Treatment began 10 weeks prior to F0 mating. Treatment-related effects were not indicated. Reproductive parameters (fertility, mating, days between pairing and mating, gestation, parturition, litter size, sex ratios, pup mortality), parental toxicity (bodyweight gain, food consumption, clinical condition, anatomic pathology), neonatal toxicity (pup bodyweight, clinical condition), and markers of endocrine function (estrus cycling, balanopreputial separation, vaginal opening, spermatogenic function, and capacity) were not effected by treatment. The high dose level met limit test conditions. No adverse effects. Chronic, reproductive, and neonatal NOEL = 15000 ppm (1038 and 1430 mg/kg/day for males and females respectively generations combined). Acceptable. (Green and Gee, 8/7/03).

TERATOLOGY, RAT

**52939-089 203989, "Rat Oral Developmental Toxicity (Teratogenicity) Study", (Dr. Th. Hofmann, Hoechst Marion Roussel, Global Preclinical Development - Germany, Drug Safety, Frankfurt am Main, Germany, Report number 97.0320, 18 February 1998). 23 mated Hoe: WISKf(SPF71) Wistar female rats per group received Hoe 130360 (AE F130360) technical (98.4% foramsulfuron) by oral gavage at 0 (1% methylcellulose in deionized water), 5, 71, and 1000 mg/kg/day on gestation days 7 through 16 (days 6-15 by FIFRA guidelines schedule). No treatment-related effects were noted for clinical signs, food consumption, bodyweight, uterine weight, litter size, sex ratios, fetal weight, early or late resorptions, and teratology at the high dose. Maternal and developmental NOEL = 1000 mg/kg/day. Limit test conditions were demonstrated. No adverse effects. Acceptable. (Green and Gee, 8/8/03).

TERATOLOGY, RABBIT

52939-090 203990, "Rabbit Oral Developmental Toxicity (Teratogenicity) Study", (Th. Hofmann, Hoechst Marion Roussel, Global Preclinical Development - Germany, Drug Safety, Frankfurt am Main, Germany, Report number 97.0295, 17 December 1997). 15 mated female Chbb: HM(SPF) Kleinrusse (Himalayan) rabbits per group received Hoe 130360 (AE F130360) (98.4% foramsulfuron) by oral gavage at 0 (1% w/v methylcellulose in water), 5, 50, and 500 mg/kg/day on gestation days 6 through 18. Maternal food consumption was reduced during treatment (gestation days 6-19) at 500 mg/kg/day. Maternal bodyweight gain was reduced during the treatment period at the high dose level. Maternal NOEL = 500 mg/kg/day. No treatment-related findings were reported for the fetuses. Developmental NOEL = 500 mg/kg/day. No adverse effects, no teratology. Not acceptable (Inadequate dose level). (Green and Gee, 8/6/03).

GENE MUTATION

**52939-083 203980, "*In Vitro* Chinese Hamster Lung V79 Cell HPRT Mutation", (W. Müller, Hoechst AG, Hoechst Marion Roussel, Preclinical Development Germany, Drug Safety, Frankfurt am Main, Germany, Study # TOX 96109, 5 December 1996). Chinese hamster lung V79 cells were exposed, in the presence and absence of rat liver S9, to Hoe 130360 technical (98.4% foramsulfuron) at 0 (untreated), 0 (ethanol), 250, 500, 1000, and 2000 µg/ml for 4 hours. Two independent trials were conducted with 7-day expression periods. Five replicate flasks were plated for mutant frequency. Precipitation was observed at 2000 µg/ml. No toxic effects were seen to the limit of solubility. No increase in the mutation frequency. Positive controls were functional. Acceptable. (Green and Gee, 8/1303).

**52939-081 203978, "Bacterial Reverse Mutation Test", (Dr. W. Muller, Hoechst AG, Hoechst Marion Roussel, Preclinical Development Germany, Drug Safety, Frankfurt am Main, Report # 96.0667, AgrEvo # 96105, 10 October 1996). Triplicate cultures of *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* WP2uvrA were exposed to Hoe

130360 (98.4% foramsulfuron), in the presence and absence of rat liver S9, at concentrations of 0 (untreated), 0 (ethanol), 0.032, 0.16, 0.8, 4, 20, 100, 500, 2500, or 5000 µg/plate for 48 hours in two independent assays. No treatment-related increase in the number of revertant colonies. Positive controls were functional. Acceptable. (Green and Gee, 8/11/03).

CHROMOSOME EFFECTS

****52939-084 203981**, "Mouse Micronucleus Test", (W. Müller, Hoechst AG, Hoechst Marion Roussel, Preclinical Development Germany, Drug Safety, Frankfurt am Main, Germany, Report # Tox 96108, 27 January 1997). 5 SHOE:NMRI mice per sex per group (for each sampling time) received a single dose of Hoe 130360 (AE F130360) technical (98.4% foramsulfuron) by oral gavage at 0 (1% methylcellulose), 200, 1000, and 2000 mg/kg. Bone marrow sampling was performed 12, 24, and 48 hours post-dosing. 1000 PCE's were scored per animal for micronuclei. The ratio of PCE/NCE was recorded and were comparable. The positive control, cyclophosphamide, was functional. No increase in micronucleated polychromatic or normochromatic erythrocytes. Acceptable. (Green and Gee, 8/13/03).

****52939-082 203979**, "In Vitro Human Lymphocyte Chromosome Aberrations", (J. Kitching, Huntingdon Life Sciences Limited, Huntingdon, Cambridgeshire, England, Study # TOX 96106, 24 January 1997). Duplicate cultures of pooled human (males) lymphocytes in whole blood were exposed to Hoe 130360 technical (98.4% foramsulfuron), in the presence and absence of rat liver S9, at concentrations of 0 (ethanol), 18.8, 37.5, 75.0, 150, 300, 600, 1200, or 2400 µg/ml. There were duplicate cultures per concentration with three trials at 2400 µg/ml. Test article was added to 48-hour cultures stimulated with PHA. Exposure -S9 was for 21 hours and 45 hours. With S9, treatment was for 3 hours followed by 18-hour or 42-hour incubation after removal of the foramsulfuron. At 150 µg/ml and higher, a precipitate formed at dosing, but was generally not apparent at the end of the treatment period. A slight increase in the number of aberrant cells was noted at 2400 µg/ml in the absence of activation. Positive controls were functional. Acceptable. (Green and Gee, 8/12/03).

DNA DAMAGE

****52939-085 203982**, "In Vivo Rat Hepatocyte Unscheduled DNA Synthesis", (K. Stocker, Huntingdon Life Sciences Ltd., Huntingdon, Cambridgeshire, England, Study # 96107, 16 September 1996). 5 male Hsd/Ola Sprague-Dawley rats per group per sampling time received a single dose of Hoe 130360 technical (98.4% foramsulfuron) by oral gavage at 0 (1% methylcellulose), 600, and 2000 mg/kg with sampling 2 and 14 hours after treatment. Hepatocytes were isolated, incubated with ³H-thymidine for 4 hours followed by 24 hours with unlabelled thymidine. A total of 150 cells per animal were evaluated for net nuclear grain counts. Four animals per test group were analyzed. No increase in unscheduled DNA synthesis was indicated. Positive controls (dimethylnitrosamine for 2 hours, 2AAF for 14 hours) were functional. Acceptable. (Note: an OECD draft guideline was used to perform this study). (Green and Gee, 8/13/03).

METABOLISM STUDIES

****52939-066 203946**, "[¹⁴C] - AE F130360, Rat: Absorption, Distribution and Elimination - Repeat Oral Dose (10 mg/kg day)", (C.M.M Reynolds, AgrEvo UK Limited, Toxicokinetics, Essex, England; Report # TOX/99/262-41, 20 December 1999). 12 Sprague Dawley CRL:(IGS) CD BR rats per sex received single daily oral (gavage) doses of [¹⁴C]-phenyl AE F130360 at 10 mg/kg for up to 14 days. 3 animals per sex were sacrificed 24 hours after 1, 9, and 14 days of treatment.

The majority of tissues were found to have residue levels below 0.01 µg AE F130360/g 24 hours after a single oral dose. Liver contained the highest concentrations of residues (0.079 µg/g and 0.114 µg/g for males and females respectively). 24 hours after the last of 14 daily doses, residues in tissues were mostly below 0.03 µg/g, except for testes (0.073 µg/g), skin (0.042 µg/g in

males and 0.166 µg/g in females), and liver (0.222 µg/g and 0.280 µg/g for males and females respectively).

Elimination of [¹⁴C]-phenyl AE F130360 and its metabolites 48 hours after repeated daily dosing for 14 days was mainly in the feces where 60.99 ± 22.19% (males) and 88.4 ± 5.21% (females) of recovered radioactivity was found.

Urine was a minor route of elimination. 4.00% (males) and 5.27% (females) was present as parent compound, AE F130360, 48 hours after daily dosing for 14 days. Cleavage product AE F153745 (4-formylamino-N,N-dimethyl-2-sulfamoyl-benzamide) accounted for 4.08% (males) and 2.41% (females), and, the free amine, AE F130619 (4-amino-2-3[-(4, 6-dimethoxypyrimidin-2-yl)-ureidosulfonyl]-N,N dimethylbenzamide), made up 3.50% (males) and 1.65% (females) of recovered label. Acceptable. (Green and Gee, 9/10/03).

**52939-065 203945, "Metabolism in the Rat Following a Single Oral Administration of 10 and 1000 mg/kg Body Weight", (R.M. Nickson, AgrEvo UK Limited, Toxicokinetics, Chesterford Park, Saffron Walden, Essex, England; Report # TOX/99/262-38, 28 October 1999). 4 Sprague Dawley CRL:CD (SD) BR rats per sex per group received a single oral (gavage) dose of [¹⁴C]-phenyl labelled AE F130360 at 10 and 1000 mg/kg. Another 2 animals per sex were dosed by gavage with [¹⁴C]-pyrimidyl labelled AE F130360 at 10 mg/kg. Urine and feces were collected separately at 6 (urine only), 12 (urine only), 24, 48, and 72 hours post-dosing for quantification of radioactivity. Expired air was not sampled since preliminary work indicated this was a minor route of excretion. The majority of the administered dose irrespective of dose level, sex, or radiolabel was excreted as unchanged parent compound in the feces.

Over the 72 hour period following dosing with [¹⁴C]-phenyl labelled AE F130360 at 10 mg/kg, 73.999% (males) and 72.337% (females) of the administered dose was found in feces as AE F130360. Cleavage product AE F153745 (4-formylamino-N,N-dimethyl-2-sulfamoyl-benzamide) accounted for 8.417% and 8.671% in males and females respectively, and, a polar unknown, made up 0.176% and 0.095% respectively. The majority was excreted during the first 24 hours, except for the polar unknown, most of which was found at 48 hours.

Cleavage product AE F153745 was the most prevalent metabolite in urine, accounting for 2.250% (males) and 2.300% (females) of administered phenyl radiolabel (10 mg/kg) over 72 hours. Parent compound, AE F130360, was 1.723% (males) and 2.128% (females). Free amine, AE F130619 (4-amino-2-3[-(4, 6-dimethoxypyrimidin-2-yl)-ureidosulfonyl]-N,N dimethylbenzamide), was found as 0.831% (males) and 0.777% (females) of administered dose. The polar unknown was present at 0.023% for both sexes. The majority was excreted 6 hours post-dosing. The polar unknown was found at 48 hours.

At 1000 mg/kg of [¹⁴C]-phenyl labelled AE F130360, 80.360% (males) and 77.732% (females) was excreted in feces as AE F130360 over 72 hours. The polar unknown accounted for 5.856% (males) and 5.637% (females); AE F153745 for 3.381% (males) and 1.264% (females); and AE F130619 for 0.489% (males) and 2.773% (females). The majority of each compound was excreted 24 hours post dosing.

Mean percentages of administered label in urine during the 72 hours following dosing with [¹⁴C]-phenyl labelled AE F130360 at 1000 mg/kg were: 0.429% as AE F130360 (both sexes); 0.239% (males) and 0.330% (females) as AE F153745; 0.313% (males) and 0.292% (females) as AE F130619; and 0.027% (males only at 48 hours) as polar unknown. Peak values for parent compound occurred 24 hours post dosing, at 6 hours for AE F153745 (both sexes), and at 6 hours (males) and 12 hours (females) for AE F130619.

24 hours after dosing with [¹⁴C]-pyrimidyl labelled AE F130360 at 10 mg/kg, the only compound detected in feces was AE F130360 at 73.204% (males) and 73.381% (females) of administered

radiolabel.

The polar unknown accounted for 3.891% (males) and 3.616% (females) of the pyrimidyl label in urine 24 hours after dosing (10 mg/kg). The free amine, AE F130619, was recovered at 2.613% (males) and 2.466% (females); and AE F130360 was 2.068% (males) and 2.989% (females) of administered dose. Peak values were recorded at 6 hours post-dosing. Pyrimidyl labelled samples were not analyzed beyond 24 hours. Acceptable. (Green and Gee, 9/10/03).

**52939-064 203944, "Tissue Distribution and Clearance in the Rat", (T. Hardwick, Covance Laboratories Ltd., Otley Road, Harrogate, North Yorkshire, England, CLE Report # 194/201 - D1141, AgrEvo Report no. TOX/99/262-43, 4 October 1999). 15 Sprague Dawley (CrI:CD BR) rats per sex per group received a single oral (gavage) dose of AE F130360 - [phenyl-U-¹⁴C] at 10 and 1000 mg/kg. 3 per sex per group were sacrificed at 0.5, 1, 4, 12, and 30 hours post-treatment. Blood, liver, spleen, lung, muscle (quadriceps), eyes, bone, thyroid, gastrointestinal tract and contents, kidney, heart, brain, testes, ovaries, adrenals, fat, and residual carcass were analyzed for radioactivity at each time point.

Radioactivity was absorbed and distributed into most tissues within 30 minutes of treatment. Maximum tissue concentrations were attained 4 and 12 hours post-dosing at 10 and 1000 mg/kg respectively.

Concentrations of radioactivity in plasma were 1½ times greater than in whole blood throughout the study. Plasma concentrations peaked at 30 minutes and 1 hour in males and females respectively at 10 mg/kg and at 4 hours in the 1000 mg/kg group. Recoveries from blood and plasma were less than 1% of administered dose at all time points for both treatment levels. Terminal elimination half-lives for plasma were determined as 18.5 hours (males) and 5.4 hours (females) and, those for blood, as 11.4 hours (males) and 4.1 hours (females) at 10 mg/kg. At 1000 mg/kg, plasma half-lives were 2.4 hours for males and 2.9 hours in females, and, for blood, 2.2 hours in females (half-life in males could not be determined).

Recovery of the majority of the administered dose at 10 and 1000 mg/kg was associated with the gastrointestinal tract at all time points (> 90% at ½, 1, and 4 hours; < 22% at 12 hours; and < 5% at 30 hours). Tissue concentrations of radioactivity were generally highest in liver at most time points and were never more than 2% and 1% of administered dose at 10 and 1000 mg/kg respectively. At 10 mg/kg, concentrations in liver ranged from 0.078 to 4.875 µg equivalents of AE F130360/g of tissue, and, at 1000 mg/kg, the range was 3.842 to 65.65 µg equivalents of AE F130360/g of tissue. High variation between concentration values in the aliquots for eyes, ovaries, thyroids, and adrenals was reported at 1000 mg/kg, however, as a percentage of administered dose, they were in the not detectable range. Acceptable. (Green and Gee, 9/10/03).

**52939-062 203942, 203943, "(¹⁴C)-AEF 130360: A Study of Excretion Following Oral Administration to Bile Duct Cannulated Rats", (K. F. Thornley, Covance Laboratories Limited, Otley Road, Harrogate, North Yorkshire, England, Report # 194/170-D1141, 3 June 1998). 6 bile duct cannulated male Sprague Dawley (CrI:CD[®]BR) rats received a single oral (gavage) dose of AE F130360 [phenyl-U-¹⁴C] at 10 mg/kg. Four animals were selected for evaluation based on the production of bile. Urine and feces along with cage debris and cage washings were collected pre-dose, 24, and 48 hours post-dosing. Bile was collected at pre-dose, 2, 4, 6, 12, 24, and 48 hours post-treatment. Animals were then sacrificed and the radioactivity as percentage of administered dose was quantified for the carcass. Approximately 17% of the administered dose was absorbed. The largest part of that was found in the urine (12.67% ± 3.7). Bile accounted for about a quarter (4.198% ± 1.872). The majority of the administered dose was not absorbed, 75.63% ± 10.64 was excreted in the feces. Acceptable. (Green and Gee, 9/9/03).

**52939-061 203941, "(¹⁴C)-AE F130360: Rat - Absorption, Distribution, Elimination Following Oral Dosing at 10 and 1000 mg/kg Bodyweight", (R. M. Nickson, Toxicokinetics, AgrEvo UK

Limited, Chesterford Park, Saffron Walden, Essex, England, Report # TOX/98/262-29, 1 July 1999). 4 Sprague Dawley CRL:CD (SD) BR rats per sex per group received a single oral gavage dose of ^{14}C phenyl labelled AE F130360 technical (98.4% foramsulfuron) at 10 and 1000 mg/kg. After dosing, animals were placed in all glass metabolism cages for 72 hours. Urine was collected 6, 12, 24, 48, and 72 hours post-dosing; feces at 24, 48, and 72 hours. The majority of the radioactivity was excreted in the feces. At 10 mg/kg, 89.97% \pm 1.24 and 89.50% \pm 1.26 of the dose was excreted in feces of males and females respectively. At 1000 mg/kg the percentages were 94.43% \pm 3.16% (males) and 97.13% \pm 0.72 (females). Most fecal excretion occurred within 24 hours after treatment.

At 10 mg/kg, 5.07% \pm 1.18 and 5.82% \pm 0.60 of the dose was excreted in the urine of males and females respectively over the three day period. At 1000 mg/kg, the percentages were 1.30% \pm 0.38 (males) and 1.46% \pm 0.41 (females) over the same time period. Most of the urinary excretion occurred in the first 12 hours.

Animals were sacrificed 3 days after dosing and tissue residues were quantified. At 10 mg/kg, most of the residues were below 0.001 mg/kg and the majority of residues were below 1.0 mg/kg at 1000 mg/kg. Liver contained 0.5 mg/kg in both sexes. Residues remaining in the carcass were less than 0.25 mg/kg for both sexes.

Total recovery of radiolabelled material 72 hours after dose administration was approximately 95% for both sexes at 10 mg/kg and 95% (males) to 99% (females) at 1000 mg/kg. Acceptable. (Green and Gee, 9/9/03).

**52939-060 203940, "Preliminary Toxicokinetic Studies in the Rat", (R. M. Nickson, Toxicokinetics, AgrEvo UK Limited, Chesterford Park, Saffron Walden, Essex, England, Report # TOX/98/262-28, 21 June 1999). In the elimination phase, 2 Sprague Dawley CRL:CD(SD)BR rats per sex per group received a single oral (gavage) dose of either ^{14}C phenyl or ^{14}C pyrimidyl labelled compound (AE F130360 technical (98.4% foramsulfuron)), at 10 mg/kg. A further one per sex received a single dose of the ^{14}C phenyl labelled material at 1000 mg/kg. Animals were maintained in glass metabolism cages for 7 days following treatment and were then sacrificed to determine residue levels in tissues. In the blood profile phase, 4 rats per sex per group received a single oral dose of the ^{14}C phenyl material at 10 and 1000 mg/kg. Blood was collected 0.5, 1, 2, 4, 6, 8, 12, 16, 20, 24, 30, 48, and 72 hours after dosing to quantify radioactive residue levels. Another 1 per sex received a single dose at 10 mg/kg with sacrifice 1 hour later to determine blood levels at the peak concentration time.

Animals showed no symptoms at either dose level. Most radioactivity was accounted for in the first 6 hours after dosing irrespective of dose level, sex, or radiolabel. Fecal elimination accounted for 85% of administered dose regardless of sex or label at 10 mg/kg and for 95% at 1000 mg/kg. Urine accounted for 10% and 5% of the administered dose at 10 and 1000 mg/kg respectively irrespective of radiolabel or sex. Urinary metabolites were identified as parent compound (AE F130360), cleavage product (AE F153745 (4-formylamino-N,N-dimethyl-2-sulfamoyl-benzamide), phenyl label only), the free amine (AE F130619 (4-amino-2-[3-(4,6-dimethoxypyrimidin-2-yl)-ureidosulfonyl]-N,N dimethylbenzamide), and an unidentified polar metabolite (pyrimidyl label only). Fecal radioactivity consisted of parent compound and cleavage product (AE F153745; phenyl label only). Plasma contained parent compound only regardless of sex. At sacrifice, phenyl and pyrimidyl labelled tissue residues were mostly below the limit of quantification.

Maximum blood concentrations were achieved at 1 hour post-dosing for both sexes at 10 and 1000 mg/kg. Blood concentrations of radiolabelled material declined biphasically with terminal half-lives of 61.4 hours (males) and 78.7 hours (females) at 10 mg/kg and a mean terminal half-life of 56.6 hours at 1000 mg/kg for both sexes. Less than 0.1% of the dose was exhaled as ^{14}C -labelled carbon dioxide during the first 48 hours. Acceptable. (Green and Gee, 9/9/03).

SUBCHRONIC TOXICITY STUDIES

52939-0073; 203953; "Hoe 130360 (AE F130360) Code: Hoe 130360 00 ZC90 0001, Rat 28 Day Dietary Repeat Dose Study"; (M. McFarlane; AgrEvo UK Limited, Toxicology Function, Saffron, Walden, Essex CB10 1XL, England; Study ID. TOX 95405; 2/27/98); Five Sprague-Dawley rats/sex/group were dosed in the diet with 0, 1000, 5000 or 20000 ppm of Hoe 130360 Technical (batch no. H 2022/1; purity: 90.0%) for 29 (F) or 30 days ((M) 0, 92, 434, 1789 mg/kg/day, (F) 0, 97, 490, 1884 mg/kg/day). No deaths resulted from the treatment. There was no apparent treatment-related effect upon the mean body weights or food consumption over the course of the study. The mean hemoglobin concentration and % methemoglobin of the 20000 ppm females were greater than those of the controls ($p < 0.01$). There were no treatment-related effects indicated by the clinical chemistry, ophthalmology, necropsy or histopathology. **No adverse effects effects indicated. Subacute NOEL:** (M/F) 20000 ppm ((M) 1789 mg/kg/day, (F) 1884 mg/kg/day) (based upon the lack of treatment-related effects in the highest dose tested); **Study supplemental** (non-guideline study) (Moore, 7/23/03)

52939-0080; 203974; "Rat 28-Day Dermal Toxicity Study, Hoe 130360 (AE F130360) Code: HOE 130360 00 (AE F 130360) 00 1C94 0001; (M. McFarlane and P. Higgs; AgrEvo UK Limited, Toxicology, Saffron, Walden, Essex CB10 1XL, England; Study ID. 96128; 9/8/99); The skin of five Sprague-Dawley rats/sex/group was treated with 0 (aqueous 1% (w/v) methyl cellulose), 10, 100 or 1000 mg/kg/day of Hoe 130360 Technical (code/batch no. AE F130360 00 1C94 0001 1/97, purity: 94.2%) for 6 hours/day for 4 weeks under an occlusive wrap. No deaths resulted from the treatment. The mean body weights and food consumption were not affected by the treatment. There were no treatment-related effects upon the results of the hematology, clinical chemistry, necropsy, or histopathology. **No adverse effect indicated. Subacute Dermal systemic NOEL:** (M/F) > 1000 mg/kg/day (based upon the lack of treatment-related effects on the 1000 mg/kg treatment group); **Dermal Irritation NOEL:** >1000 mg/kg/day (based upon the lack of treatment-related effects on the 1000 mg/kg treatment group); **Study acceptable.** (Moore, 8/4/03)

52939-0074; 203954; "Hoe 130360 (AE F130360) Code: Hoe 130360 00 ZC90 0001, Mouse 28-Day Dietary Toxicity"; (M. McFarlane and N.A.P.S. Buss; AgrEvo UK Limited, Toxicology, Saffron, Walden, Essex CB10 1XL, England; Study ID. TOX 95385; 1/29/98); Five CRL:CD-1 (ICR) BR mice/sex/group were dosed in the diet with 0, 400, 1600 or 6400 ppm of Hoe 130360 Technical (batch no. H 2022/1; purity: 90.0%) for at least 28 days ((M) 0, 51.5, 312, 1164 mg/kg/day, (F) 0, 62.5, 401, 1695 mg/kg/day). No deaths resulted from the treatment. There was no apparent treatment-related effect upon the mean body weights or food consumption over the course of the study. In the hematology, the mean number of platelets for the 400 ppm females and above was lower than that of the controls ($p < 0.05$ or 0.01). The mean serum sodium and chloride concentrations of the 6400 ppm females were lower those of the control ($p < 0.05$ and $p < 0.01$, respectively). There were no apparent treatment-related effects indicated by the necropsy or histopathology results. **No adverse effect indicated. Subacute NOEL:** (M/F) 6400 ppm ((M) 1164 mg/kg/day, (F) 1695 mg/kg/day) (based upon the lack of treatment-related effects at the highest dose tested); **Study acceptable.** (Moore, 7/24/03)

52939-0075; 203966; "Hoe 130360 (AE F130360) Code: Hoe 130360 00 ZC98 0001, Dog 28-Day Oral Toxicity Study"; (S.M. Wason and N. Buss; AgrEvo UK Limited, Toxicology Function, Saffron, Walden, Essex CB10 1XL, England; Study ID. TOX 95386; 12/18/98); Two beagle dogs/sex/group were dosed orally by gavage with 0 (aqueous 0.5% (w/v) methyl cellulose), 40, 200 or 1000 mg/kg/day of Hoe 130360 (AE F130360) Technical (batch no. H 2037; purity: 98.4%) for at least 28 days. There was no treatment-related effect upon body weight changes or food consumption. The ophthalmology, hematological, biochemical and urinalysis results did not indicate any treatment-related effects. No apparent treatment-related effect were indicated by the necropsy examination, organ weights or the histopathology. **No adverse effects indicated. Subacute NOEL:** (M/F) > 1000 mg/kg/day (based upon the lack of treatment-related effects in the 1000 mg/kg treatment group); **Study supplemental** (non-guideline study). (Moore, 8/1/03)

52939-0076; 203968; "Hoe 130360 (AE F130360) Code: Hoe 130360 00 ZC97 0001, Rat 90-Day Dietary Toxicity Study with 4 Week Off Dose Period"; (M. McFarlane and N.A.P.S. Buss; AgrEvo UK Limited, Toxicology Function, Saffron, Walden, Essex CB10 1XL, England; Study ID. TOX 95387; 1/29/98); Ten Sprague-Dawley Crl:CD (SD) BR rats/sex/group received in the diet 0, 20, 200, 5000 or 20000 ppm of Hoe 130360 Technical (batch no. H 2027/1; purity: 997.4%) for 13 weeks ((M) 0, 1.54, 15.4, 388, and 1568 mg/kg/day, (F) 0, 1.81, 19.4, 475, 1786 mg/kg/day). An additional 10 animals/sex/group received 0 or 20000 ppm of the test material for 13 weeks and then were maintained on a control diet for an additional 4 weeks. There were no test material-related deaths during the study. The mean body weights and food consumption were not affected by the treatment. No apparent treatment-related effects were noted in the ophthalmoscopy examination, hematology, clinical biochemistry or urinalysis. No treatment-related effects were evident in the organ weights, gross examination or histopathology. **No adverse effect indicated. Subchronic NOEL (M/F):** >20000 ppm ((M) 1568 mg/kg/day, (F) 1786 mg/kg/day) (F) 1786 mg/kg/day) (based upon the lack of treatment-related effects in the 20000 ppm treatment group). **Study acceptable.** (Moore, 7/31/03)

52939-0077; 203971; "Hoe 130360 (AE F130360) Code: Hoe 130360 00 ZC98 0001, Mouse 90-Day Dietary Toxicity"; (L.R. Weir and M. McFarlane; AgrEvo UK Limited, Toxicology Function, Saffron, Walden, Essex CB10 1XL, England; Study ID. TOX 95388; 4/3/98); Ten Crl: CD-1 (ICR) BR mice/sex/group were dosed in the diet with 0, 64, 3200 or 6400 ppm of Hoe 130360 Technical (batch no. H 2037; purity: 98.4%) for 90 days ((M) 0, 10.5, 498, 1002 mg/kg/day, (F) 0, 14.6, 822, 1178 mg/kg/day). No treatment-related deaths occurred during the study. There was no treatment-related effect upon the mean body weights or food consumption. Although some of the hematology and clinical chemistry parameters of the treated groups differed from those of the controls, either the difference was within the historical control range or a dose-response was not evident. There was no apparent treatment-related effect indicated by the necropsy results. In the histopathology examination, the only apparent treatment-related effect was the incidence of basophilic tubules in the 6400 ppm males (0: 0/10, 6400: 4/10). The effect has no apparent toxicological significance. **No adverse effect indicated. Subchronic NOEL (M/F)** > 6400 ppm ((M) 1002 mg/kg/day, (F) 1178 mg/kg/day) (based upon the lack of treatment-related effects in the 6400 ppm group); **Study acceptable.** (Moore, 7/25/03)

52939-0078; 203972; "Hoe 130360 (AE F130360) Code: AE F130360 00 1C93 0001, Dog 90-Day Oral Toxicity Study"; (P. Higgs; AgrEvo UK Limited, Toxicology Function, Saffron, Walden, Essex CB10 1XL, England; Study ID. TOX 95406; 9/15/98); Four beagles/sex/group were treated orally by gavage with 0 (aqueous 0.5% (w/v) methyl cellulose), 10, 250, or 1000 mg/kg/day of Hoe 130360 (AE F130360) Technical (batch no. 2/96; purity: 94.1%) for 13 weeks. There was no treatment-related effect on mean body weights. The mean food consumption of the 1000 mg/kg females was lower than that of the controls (0: 369.9 (\pm 20.1) vs. 1000: 346.2 (\pm 17.7) g/animal/day). No treatment-related effect was noted in the ophthalmoscopy. There was no treatment-related effect on the hematology or clinical chemistry results. No apparent treatment-related effects were indicated by the gross necropsy, organ weights, or histopathological results. **No adverse effect indicated. Subchronic NOEL:** (M/F) > 1000 mg/kg/day (based upon the lack of treatment-related effects in the 1000 mg/kg/day treatment group); **Study acceptable.** (Moore, 8/1/03)