

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
IODOSULFURON-METHYL-SODIUM (named AE F115008 or Hoe 115008)

Chemical Code # 6015, Document Processing Number (DPN) # 53099
SB 950 # Not applicable
Original date: 12/13/10
Revised date: Not applicable

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
Developmental toxicity, rat:	No data gap, no adverse effect
Developmental toxicity, 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 for study reports of the above study types through Document No. 53099-0015, Record No. 253752 were examined. This includes all relevant studies indexed by DPR as of Oct. 7, 2010.

In the 1-liners below:

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

indicates a study on file but not yet reviewed.

File name: t20101213.wpd

Original by Aldous, 12/13/10. Revised by Name, Date: (Not applicable)

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

COMBINED, RAT

**53099-0008 249654 Wason, S. M., "AE F115008 (Hoe 115008) Code: AE F115008 00 1C89 0001 Rat dietary combined chronic toxicity and oncogenicity study," AgrEvo UK Ltd., Essex, England, 10/23/98, Laboratory Study # Tox 94468. Groups of 60 Crl:CD (SD) BR rats/sex/group received Iodosulfuron-methyl-sodium Technical (named AE F115008 or Hoe 115008), 88.7% purity, for 104 weeks in a combined chronic/oncogenicity study at 0, 70, 700, or 7000 ppm. Estimated achieved intake for lifetime study rats was 3.0, 30, and 331 mg/kg/day for males and 3.9, 39, and 452 mg/kg/day for females. An additional 10/sex/group were treated for 1 year prior to sacrifice. NOEL for males = 70 ppm, based on marginal decrements in body weight (8% body weight decrement at termination for 700 ppm males). NOEL for females = 700 ppm, based principally on significant body weight decrements. Body weights were reduced by 14% and 22% in 7000 ppm males at 1-yr and 2-yr weight measurements. High dose females showed 15% and 24% decrements in body weight at those intervals. Modest food consumption decrements were noted in both sexes during the first few weeks on treatment at 7000 ppm. Treatment had no influence on tumor incidences. Lobular atrophy of submandibular glands was restricted to 7000 ppm rats of both sexes (7 males and 5 females: "minimal" to "slight" degree). This was evidently treatment-related, but of apparently inconsequential toxicological importance. Study is acceptable, with no adverse effects. Aldous, July 2, 2010.

NOTE: the pathology segments for the 12-mo and 24-mo segments of the report, contained in and continuous with the rest of the present report, were given additional DPR record numbers (249665 and 249666, in report parts 2 and 3, respectively). The latter segments had independent pagination from the rest of the report.

CHRONIC TOXICITY, RAT

See Combined, Rat (above).

CHRONIC TOXICITY, DOG

53099-0015 253752 Wason, S. M., "AE F115008 (Hoe 115008) Code: AE F115008 00 1C89 0001: Dog 12 month oral (dietary) toxicity study," AgrEvo UK Ltd., Essex, England, 8/20/98. Laboratory Study # Tox 94466. Groups of 6 beagles were dosed in diet at 0, 30, 200, or 1200 ppm of Iodosulfuron-methyl-sodium Technical (Hoe 115008), 88.7% purity, for 52 weeks. Estimated achieved dose levels were 1.0, 7.4, and 42 mg/kg/day in males, and 1.1, 7.2, and 44 mg/kg/day in females. NOEL in males = 1200 ppm (highest dose tested). NOEL in females = 200 ppm (elevated blood cholesterol, significant only at 6 months; and generalized hematopoietic hyperplasia in bone marrow, most commonly of "slight" degree). Note that moderate hematotoxicity had been observed at 1200 ppm in the rat subchronic study (Record No. 249646). **Acceptable, with no adverse effects. Aldous, 9/15/10.

53099-0014 249853 This is an exact duplicate of 53099-0015 253752, above.

ONCOGENICITY, RAT

See Combined, Rat (above).

ONCOGENICITY, MOUSE

**53099-0007 249653 Wason, S. M., "AE F115008 (Hoe 115008) Code: AE F115008 00 1C89 0001 Mouse dietary 18 month oncogenicity study," AgrEvo UK Ltd., Essex, England, 10/23/98. Laboratory Study # Tox 94467. Groups of 60 CD-1 mice/sex/group were dosed in diet with 0 or 1750 ppm Iodosulfuron-methyl-sodium Technical (named AE F115008 or Hoe 115008), 88.7% purity, in an 80-wk oncogenicity study. Groups of 50 mice/sex/group were dosed with 35 or 350 ppm AE F115008 for the same period. Achieved dose levels were 5.2, 54, and 279 mg/kg/day for low to high-dose males, and 5.7, 58, and 277 mg/kg/day for corresponding females. NOEL for males = 35 ppm and NOEL for females = 350 ppm, each displaying slight liver centrilobular hepatocellular enlargement at the LOEL. High dose males and females had liver weight increases of 27% and 12% over controls, respectively. High dose males had marked centrilobular changes including hepatocellular enlargement, pigmentation, fatty deposits, and increased mononuclear cell infiltration. Study is acceptable, with no adverse effects. Aldous, July 2, 2010.

REPRODUCTION, RAT

53099-0006 249652 Horstmann, G., "Hoe 115008 - Substance Technical (Code: Hoe 115008 00 ZC89 0001) Two-generation feeding-reproduction toxicity study in rats," HMR Deutschland GmbH, Hattersheim, Germany, Nov. 9, 1998. Laboratory Study # 98.0762. Groups of 25 Wistar [Hoe:WISKf(SPF71)] rats/sex were dosed in diet with Iodosulfuron-methyl-sodium Technical (named Hoe 115008 in this report), 88.7% purity, in a standard reproduction study. Estimated pre-mating mean compound intakes for low to high dose parental rats were 3.4, 34, and 347 mg/kg/day for F0 males, 3.9, 40, and 390 mg/kg/day for F0 females, 4.8, 49, and 506 mg/kg/day for F1 males, and 5.3, 53, and 541 mg/kg/day for F1 females. Higher achieved mean dose levels in the F1 generation reflects different onset of dosing period (about 7 wks of age for F0 vs. 3 wks for F1: pre-mating durations being 10 wks for F0 and 14 wks for F1). Parental systemic toxicity NOEL = 500 ppm (slight body weight decrements in P1 males, marginal body weight decrements in F0 dams during gestation, and in F1 dams during lactation, and apparent increase in kidney pelvic dilatation). Parental reproductive effects NOEL = 5000 ppm (no reproductive effects detected). Offspring viability and growth NOEL = 500 ppm [based on high dose findings of increased resorptions, peri-natal losses indicated by increased numbers of dead fetuses in F1 offspring and modest increase in numbers of litters with one or more pups dying at PND 1 in both generations, and slight body weight decrements in pups during lactation (statistically significant only in F1 pups)]. **Acceptable, with no adverse effects, Aldous, 9/20/10.

DEVELOPMENTAL TOXICITY, RAT

53099-0004 249648 Hofmann, Th., "Hoe 115008; substance technical, Code Hoe 115008 00 ZC89 0001 Rat oral developmental toxicity (teratogenicity) study," Hoechst AG, Frankfurt, Germany, 10/23/96. Study ID's: Artemis No. RR0737; Hoechst No. A57677. Groups of 23 Hoe: WISKf(SPF71) Wistar rats were dosed on gestation days 7-16 by gavage (CMC, 1%, 5 ml/kg b.w.) with Hoe 115008 (Iodosulfuron-Methyl-Sodium Technical), purity 88.7% at 0, 100, 315, or 1000 mg/kg/day in a developmental toxicity study. Maternal NOEL = 315 mg/kg/day, based on increased salivation in 15/23 dams, compared to none in any other groups; and on modest decrease in food consumption during the dosing period. Fetal NOEL = 315 mg/kg/day, based on ossification delays in skull bones, sacral vertebral arch, sternbrae, and forepaw metacarpal No. 5. Findings of blood in the abdominal cavity and of kidney pelvic distension were statistically significantly increased in the high dose group (at least for fetal incidence). The latter were within historical range, and constitute equivocal additional indications of treatment effects. **Acceptable, with no adverse effects. Aldous, 9/23/10.

DEVELOPMENTAL TOXICITY, RABBIT

53099-0005 249650 Hofmann, Th., "Hoe 115008; substance technical, Code Hoe 115008 00 ZC89 0001 Rabbit oral developmental toxicity (teratogenicity) study," Hoechst AG, Frankfurt, Germany, 10/10/96. Artemis No. RK0733; Hoechst No. A57676. Groups of 15 Chbb: HM(SPF) Kleinrusse (Himalayan) rabbits were dosed on gestation days 6-18 by gavage (CMC, 1%, 5 ml/kg b.w.) with Hoe 115008; substance, technical, purity 88.7% in a developmental toxicity study at 0, 25, 100, or 400 mg/kg/day. All treatment groups had statistically significant and dose-related decreased food consumption during the dosing period, however only the 400 mg/kg/day does showed remarkable body weight deficit and food consumption of the 25 mg/kg/day group was within recent historical control range, hence 25 mg/kg/day is a defensible NOEL for dams. There were no effects on offspring, hence developmental toxicity NOEL > 400 mg/kg/day. **Acceptable, with no adverse effects. Aldous, 9/28/10.

53099-0005 249649 and 53099-0005 249651 provide historical control data relevant to the above rabbit developmental toxicity study.

GENE MUTATION

**53099-0009 249667 Stammberger, I., "Hoe 115008; substance, technical, (Code Hoe 115008 00 ZC97 0001) Study of the mutagenic potential in strains of *Salmonella typhimurium* (Ames test) and *Escherichia coli*," Hoechst AG, Frankfurt, Germany, 7/7/93. Laboratory Study #: 93.0343, Hoechst # A51035. Iodosulfuron-methyl-sodium (Code Hoe 115008 00 ZC97 0001, purity 97.4%). This standard reverse mutation study used strains *Salmonella typhimurium*: TA 1535, TA 100, TA 1537, and TA 98; and *E. coli*: WP2 uvrA. There were two experiments, each using treatments of 0, 4, 20, 100, 500, 2500, 5000 µg/plate with and without S-9 activation (from livers of Aroclor 1254-treated rats). There were three reps/treatment/test. Positive controls were functional. Study is acceptable, with a noted design weakness in that the second experiment did not optimize treatment levels based on results of the first experiment. Aldous, 9/13/10.

53099-0009 249674 Müller, W., "Hoe 115008; substance technical, (Code: Hoe 115008 00 ZC89 0001) *in vitro* mammalian cell gene mutation test: HPRT-test with V79 Chinese hamster cells," Hoechst AG, Frankfurt, Germany, 8/13/96. Laboratory Study # 96.0394, Hoechst # A57293. Chinese hamster V79 cells were exposed to test article [Iodosulfuron-methyl-sodium, designated as Code Hoe 115008, purity 88.7%] for 4 hrs, then allowed to grow with subculturing for 8 more days, with sampling for viability, prior to addition of 6-thioguanine as the selection agent. Initial treatment levels were 0, 100, 300, 600, 1200, 2000, and 2649 µg/ml with and without S-9 (S-9 from livers of male CD rats, pre-treated with Aroclor 1254). The two highest doses without S-9 were discontinued for the second of two mutagenicity experiments due to excessive cytotoxicity (survival only 2-3%). Viability was acceptable for all groups with S-9. There was no reproducible increase in mutation frequency with or without S-9, whereas positive controls (EMS without S-9, DMBA with S-9) were highly functional. Study is **acceptable, with no adverse effects. Aldous, July 6, 2010.

CHROMOSOME EFFECTS

53099-0010 249677 Müller, W., "Hoe 115008; substance technical (Code Hoe 115008 00 ZC89 0001): mammalian erythrocyte micronucleus test in male and female NMRI mice," Hoechst AG, Frankfurt, Germany, 8/21/96. Laboratory Study #: 96.0404, Hoechst # A57253. Five mice/sex/ dose/interval were dosed once by gavage with 0, 200, 1000, or 2000 mg/kg of iodosulfuron-methyl-sodium (Hoe 115008, 88.7%). Mice were sacrificed 12, 24, or 48 hrs after treatment. Positive control was Cyclophosphamide (Endoxan®), 50 mg/kg, gavage. This group of 5/sex was sacrificed 24 hrs after treatment. At sacrifice, bone marrow suspensions from femurs were prepared for examinations of 1000 PCE's/mouse, as well as 1000 NEC's/mouse (samples coded for blind evaluation). There were no increases in PCE's with treatment. There was a statistically significant increase in micronuclei among normochromatic cells for sexes combined at 24 hrs. This appears not to be important, since PCE's rather than NCE's are the primary stage of interest, and individual counts in these groups never exceeded 3/1000 for any 2000 mg/kg male or female. Positive controls had clear increases in micronucleated PCE's, with minimal effect on NCE's. Study is **acceptable, with no adverse effects. Aldous, July 6, 2010.

53099-0009 249675 Müller, W., "Hoe 115008; substance technical, (Code Hoe 115008 00 ZC89 0001) *in vitro* mammalian chromosome aberration test in V79 Chinese hamster cells," Hoechst AG, Frankfurt, Germany, 9/23/96. Report # 96.0542, Hoechst # A57511. Iodosulfuron-methyl-sodium. Purity was 88.7%. Non-activated, 20-hr incubation with test article at 0, 100, 250, and 500 µg/ml, and also 28-hr incubation with test article at 0 and 500 µg/ml. S-9 activated 20-hr incubation (the first 3 hrs with test article: balance of time with fresh medium for expression) was evaluated 0, 500, 1500, and 2649 µg/ml. Finally a comparable 28-hr incubation without S-9 was undertaken 0 and 2649 µg/ml. All a.i. results were negative. Positive controls (EMS at 500 µg/ml without S-9: cyclophosphamide at 3 µg/ml with S-9) were functional. Study is **not acceptable** (insufficient documentation that treatments without S-9 were conducted to the highest practical concentrations). Data with S-9 activation are usable. Aldous, July 6, 2010.

DNA DAMAGE

**53099-0010 249676 Müller, W., "Hoe 115008; substance technical (Code: Hoe 115008 00 ZC89 0001): Detection of DNA strand breaks in primary hepatocytes of male rats *in vitro*: UDS - Test in primary rat hepatocytes," Hoechst AG, Frankfurt, Germany, 10/28/96. Laboratory Study # 96.0596, Hoechst # A57977. Primary hepatocytes were obtained from male Wistar rats with the aid of collagenase and mechanical separation, followed by filtration. After cells had been allowed to attach to surfaces of culture dishes, they were exposed to test material for 16-20 hrs in the presence of [³H]-thymidine. At termination, cells were swollen with 1% sodium citrate, mounted, treated with film emulsion in a light-proof box, then stained for microscopic examination. Net nuclear grain counts were evaluated with cytoplasmic areas for reference. Iodosulfuron-methyl-sodium [Hoe 115008] at 88.7% purity was evaluated at 0.01, 0.03, 0.1, 0.3, 1, 3, 10, 30, 100, 300, 1000 µg/ml. Higher concentrations caused "morphological deformation" of the cells. Cell survival was markedly reduced at 3000 to 5000 µg/ml. There were two independent experiments, with two replicates per concentration. There were no treatment-related increases in net grain counts. Positive controls (2-AAF at 1 µg/ml) gave high net nuclear grain counts. Acceptable, with no adverse effects. Aldous, 9/14/10.

NEUROTOXICITY

53099-0010 249678 This is a 2004 waiver request in response to U.S. EPA request for an acute neurotoxicity study. The record discusses clinical signs in response to very high dose levels, such as salivation at high but survivable dose levels, and other signs at lethal levels. Registrant notes that neither this a.i. nor analogs indicate specific neurotoxicity signs. An acute neurotoxicity study was later submitted (see next record). Aldous, June 3, 2010.

53099-0010 249679 This is an U.S. EPA DER of an acute neurotoxicity study completed in 2008. The study was accepted by U.S. EPA. EPA concluded that "The NOAEL was 100 mg/kg bw for males and 500 mg/kg bw for females." Key findings were "decreased motor and locomotor activities (both sexes), decreased body temperature (female), and clinical signs of toxicity (both sexes)." This study was not submitted to DPR (and DPR had not requested such a study). Evidently the U.S. EPA reviewer did not attribute urine staining in 2/12 females at 500 mg/kg to treatment, hence EPA concluded that the NOAEL for females was 500 mg/kg, whereas the study investigators considered 500 mg/kg to be the NOAEL for both sexes, the urine staining being the most sensitive indicator in females. The DER provides data tables for the cited parameters. Useful supplementary data. Aldous (DPR review not appropriate, since this record is itself a review). June 3, 2010.

METABOLISM

Metabolic disposition studies of idosulfuron-methyl-sodium technical indicated about 80% absorption (based on percent of residues in urine). Parent idosulfuron-methyl-sodium accounted for about 80% of excreted label, and was the dominant component of urine, and major component in feces. The majority of identified metabolites retained the sulfonylurea bridge, and commonly involved oxidation of triazine ring substituents. Initial phase absorption was rapid:

$t_{1/2}$ estimates were about 4 hrs, followed by a much slower phase. About 0.5% of administered dose remained in the carcass after 72 hrs. Tissue levels at 72 hrs (following triazinyl-2-¹⁴C label) were typically at least 2.5 x higher in plasma than in other tissues, without any other remarkable affinities.

53099-0010 249680 Maas, J., "Hoe 115008: Rat: Absorption, disposition and elimination - oral high dose (500 mg/kg body weight)," Hoechst AG Kinetics & Metabolism, Frankfurt, Germany, Jan. 29, 1996. Project No. 204/1, Hoechst # A56257. Ten Wistar rats/sex were dosed once with 500 mg/kg idosulfuron-methyl-sodium (Hoe 115 008) by gavage in 10 ml/kg water as vehicle. Five per sex of these were used to evaluate disposition in tissues and excreta. The other rats were used for metabolite characterization (reported separately). ¹⁴C-label was on triazinyl-2 carbon, radiochemical purity by HPLC = 98.6%. Estimated $t_{1/2}$ for urinary excretion was 7.3 and 6.5 hrs for males and females, respectively. Corresponding fecal excretion $t_{1/2}$ estimates were 8.5 and 6.1 hrs, respectively. About 59% and 73% of administered dose was eliminated in urine in males and females during the first 24 hrs, compared with 21% and 15% of administered dose in feces. Thus about 79% and 88% of administered dose, respectively, was accountable to these routes over the first 24 hrs. Total excretion over 72 hrs was 95.6% and 95.3% in males and females. Tissues retained 0.53% of label in both sexes at 72 hrs. Highest organ and tissue concentrations were in whole blood and plasma (2.3 to 4.0 μ g equivalents/g). About one-half these levels were found in kidneys, lungs, liver, and heart. Other tissues generally had lower levels. Study is adequate for this component of the metabolism series. Aldous, July 6, 2010.

53099-0010 249681 Maas, J., "¹⁴C-Hoe 115008: Blood levels following single oral administration of 500 mg/kg body weight to male and female rats," Hoechst AG Kinetics & Metabolism, Frankfurt, Germany, 1/29/96. Project No. 204/2, Hoechst # A56258. Five Wistar rats/sex were dosed once with 500 mg/kg idosulfuron-methyl-sodium (Hoe 115 008) by gavage in 10 ml/kg water as vehicle. ¹⁴C-label was on triazinyl-2 carbon, radiochemical purity by HPLC = 97.8%. Blood samples were taken from the tail tip at intervals from 0.25 hrs to 168 hrs after dosing to assess blood kinetics profile. Results were consistent with rapid absorption, rapid initial distribution and clearance from blood, followed by slow phase clearance, without evident sex difference. The following parameters were obtained per sex (M and F, respectively): C_{max} (696 and 584 μ g equivalents/g), t_{max} (7.3 and 7.6 hrs), $t_{1/2}$ (I) (4.6 and 3.6 hrs), and $t_{1/2}$ (II) (82 and 71 hrs). Study is adequate for this component of the metabolism series. Aldous, July 6, 2010.

53099-0010 249682 Lauck-Birkel, S., "¹⁴C-triazinyl-Hoe 115008: Rat metabolism - oral high dose (500 mg/kg body weight)," Hoechst AG Kinetics & Metabolism, Frankfurt, Germany, 1/23/98. Study ID: CM95/034, Hoechst # A56609. Urine and feces samples for this study came from Project No. 204/1 (DPR Record No. 249680): a 72-hr collection period using 5 rats/sex. Quantification usually involved radio-HPLC. Investigators provided authentic standards for Hoe 115 008 and some common metabolites [Hoe 075736 (de-iodination product); Hoe 145740 (benzoic acid product of ester cleavage); and Hoe 145741 (de-alkylation of triazine methoxy group)]. Two more metabolites were characterized by MS [CH₂OH-metabolite (hydroxylation of triazine methyl substituent); and T2 (2-amino-4-hydroxy-6-hydroxymethyl-1,3,5-triazine)]. The a.i. had the longest retention of any common peaks, and had a sharp MS peak consistent with molecular structure (M-H, without the sodium: peak at 506). Hoe 115 008 test article was the dominant component of urine [51% and 69% of administered dose (AD) in M and F, respectively] and of feces (11% and 7% of AD in M and F). Percent AD of other identified

urinary metabolites in M and F were: Hoe 075736 (1.4 and 0.6), Hoe 145740 (1.3 and 0.5), Hoe 145741 (3.2 and 1.3), CH₂OH-metabolite (2.7 and 1.7), and T2 (1.4 and 0.7). Similar or slightly smaller % AD of all these metabolites were found in feces. There were several unknown metabolites in feces: none constituted a large part of the AD, and all but one were evidently more polar (shorter retention time) than a.i. and identified metabolites. Note that Hoe 145741 constituted about 1% of the technical, and that about 1% of technical was Hoe 145740 and/or Hoe 075736. Study is adequate for this component of the metabolism series. Aldous, 9/14/10.

53099-0010 249683 Maas, J., "Phenyl-U-¹⁴C-Hoe 115008: Biostability after a single oral administration of 500 mg/kg body weight to a male and a female rat" [includes Amendment # 1 to the final report]. Hoechst AG Kinetics & Metabolism, Frankfurt, Germany, 11/19/96. Project ID: TEP:204/4, Hoechst # A58727. Two rats (1/sex) were dosed with phenyl-labeled Hoe 115 008 to assess exhaled ¹⁴C-CO₂ (by gas flow counter). Administered radioactivity was > 1 x 10⁸ dpm/rat. No volatile radioactivity was found, indicating that the phenyl ring was not degraded to a detectable extent. There was, however, no parallel standard provided to assess the sensitivity of the detection system. Supplementary data for the metabolism series. Aldous, July 6, 2010.

53099-0010 249684 Lauck-Birkel, S., "U-¹⁴C-phenyl-Hoe 115008: Rat metabolism - oral high dose (500 mg/kg body weight)," Hoechst Schering AgrEvo GmbH, Frankfurt, Germany, 3/19/97. Study ID: CM96/001, Hoechst # A57610. This study is comparable to DPR Record No. 249682 (Study ID: CM95/034, Hoechst # A56609), except for the placement of the radiolabel. There were 4 rats/sex and a 72-hr collection period. See DPR review of Record No. 249682 for common metabolite descriptions. Most of a.i. was absorbed, as indicated by recovery in urine plus cage wash [71.5% and 85.5% of administered dose (AD) in M and F, respectively]: feces contained 24.5% and 14.9% of AD in M and F. Most label was collected within 24 hrs. Parent (Hoe 115 008) was the dominant component of urine. In the first 24 hrs, 44.1% and 71.6% of AD were recovered as Hoe 115 008 in urine of M and F, respectively. Hoe 115 008 recovered within 24 hrs in feces comprised 6.1% and 5.2% of AD, respectively. Percent AD of other identified urinary metabolites in M and F were: Hoe 075736 (0.5 and 0.5), Hoe 145740 (1.5 and 0.8), Hoe 145741 (2.5 and 1.7), and CH₂OH-metabolite (2.2 and 2.3). Products of sulfonylurea bridge cleavage (as % in M and F, respectively) included "P1" (2-aminosulfonyl-4-iodobenzoate), (2.5 and 1.5); and Hoe 143133 (6-iodo-1,2-benzisothiazole-3(2H)-on-1,1-dioxide), (1.2 and 0.7). Generally similar % AD of most of these metabolites were found in feces. A minor exception was that Hoe 143133 was absent or at very low levels in feces, whereas its presumed precursor [Hoe 114368 (methyl 2-aminosulfonyl-4-iodobenzoate)] was found in feces at low but detectable levels. Hoe 145741 and Hoe 145740 each constituted >1% of the technical. Study is adequate for its scope. Aldous, July 6, 2010.

53099-0010 249685 Maas, J., Dl. R. Braun, and F. Schmidtke, "[Triazinyl-2-¹⁴C] Hoe 115008: Rat: Absorption, disposition and elimination - oral low dose (10 mg/kg body weight)," Hoechst AG Pharmacokinetics, Frankfurt, Germany, Dec. 5, 1996. Project No. 204/6, Hoechst # A57608. Four Wistar rats/sex were dosed once with 10 mg/kg idiosulfuron-methyl-sodium (Hoe 115 008) by gavage in 10 ml/kg water as vehicle. Radiochemical purity by HPLC = 99.3%. Urinary excretion T_{1/2} was 4.2 and 3.9 hrs for males and females, respectively. Corresponding fecal excretion T_{1/2} estimates were 6.1 and 8.7 hrs, respectively. [The urinary excretion T_{1/2} estimates were slightly shorter than indicated for the high dose study (DPR Record No. 249680), and may represent absorption or renal secretion which was saturable at high doses.] About 97% of

administered dose was excreted in urine plus feces during the first 24 hrs, irrespective of sex. Urinary excretion predominated, with 90% and 94% of administered dose found in urine in males and females during the first 24 hrs, and 6% and 3% of administered dose via feces in that period. This proportion excreted in urine was somewhat higher than was observed in the high dose study (consistent with efficient absorption and some saturation at high dose levels). Total accounting for label in excreta over 72 hrs was 101% and 102% in males and females in urine plus feces. Tissues retained a modest 0.5% of label in both sexes at 72 hrs. Tissue concentrations were high in whole blood (0.105 and 0.079 μg equivalents/g in males and females, respectively), and especially high in plasma (0.168 and 0.129 μg equivalents/g, respectively). Concentrations in other tissues were typically less than 40% of plasma concentrations, with no tissue having strong affinity. Valid data for the scope of this study. Aldous, July 6, 2010.

53099-0011 249688 Maas, J. and DI R. Braun, “ ^{14}C -Hoe 115008: Blood levels following single oral and intravenous administration of 10 mg/kg body weight to male and female rats,” Hoechst AG Pharmacokinetics, Frankfurt, Germany, 8/20/96. Project No. TEP 204/3, Hoechst # A58313. Five Wistar rats/sex were dosed with triazinyl-2- ^{14}C -Hoe 115008 at 10 mg/kg to compare kinetics via gavage and iv routes. Assessments were limited to whole blood radiolabel analyses and associated toxicokinetics calculations. As expected, iv treatment led to immediate peak blood levels, followed by an initial first order decay $t_{1/2}$ (I) (2-3 hrs), and a later $t_{1/2}$ (II) (37-48 hrs). Gavage treatment yielded radio-level plateaus over the range of 2-8 hrs, with t_{max} estimates of 3.6 and 6 hrs for males and females (probably not a meaningful sex difference). Gavage group $t_{1/2}$ (I) and $t_{1/2}$ (II) estimates were comparable to iv values. C_{max} estimates were 64-70 μg equivalents/g in iv groups, vs. 17 μg equivalents/g in gavage groups. This relationship confirms high absorption following oral dosing. From AUC estimates, investigators determined that absorption rates were about 86% in males and 63% in females. The estimate for females is slightly lower than would be inferred from $\geq 90\%$ urinary excretion observed in both sexes in Record No. 249685, and absorption on the order of 90% is probably correct for both sexes. Study is adequate for this component of the metabolism series. Aldous, July 2, 2010.

53099-0011 249689 Lauck-Birkel, S., “2- ^{14}C -triazinyl-Hoe 115008: Rat metabolism - oral low dose (10 mg/kg body weight),” Hoechst Schering AgrEvo GmbH, Frankfurt, Germany, May 6, 1997. Study ID: CM96/040, Hoechst # A57611. Urine and feces samples for this study came from Project No. 204/6 (DPR Record No. 249685): a 72-hr collection period using 4 rats/sex. See that record or its review for kinetics results. See DPR review of Record No. 249682 for common metabolite descriptions. The present analyses were made on collections of highest specific radioactivity: urine from 0-48 hrs, and feces from 8-24 hrs (urine accounting for most of recovered label). Hoe 115 008 test article was the dominant component of urine (81% and 86% of administered dose (AD) in M and F, respectively). Percent AD of other identified urinary metabolites in M and F were: Hoe 075736 (1.3 and 1.1), Hoe 145740 (1.1 and 0.7), Hoe 145741 (2.1 and 0.9), CH_2OH -metabolite (2.8 and 1.7), and T2 (0.8 and 0.5). Most of these metabolites were found in small amounts in feces. Hoe 115 008 was also found in feces (1.9% and 1.1% of AD in M and F). There were no common uncharacterized metabolites. The higher percentage of urinary excretion compared to results of the corresponding 500 mg/kg dose of 2- ^{14}C -triazinyl-Hoe 115008 indicates a high level of absorption, which is slightly saturable at very high dose levels. Valid data for the scope of this study. Aldous, 9/13/10.

53099-0011 249690 Mass, J. and DI R. Braun, “[Phenyl-U-¹⁴C]-AE F115008: Rat absorption, distribution, elimination - repeated oral dose (7 x 100 mg/kg bw),” Hoechst Marion Roussel, Frankfurt, Germany, 3/27/98. Project No. TEP 204/9, HMR # C 000383. Groups of 3 rats/sex were killed for tissue label analysis 6 hrs after the last of either 1 or 4 consecutive daily doses. Other groups of 3 rats/sex received 7 consecutive daily doses prior to sacrifice either 6 hrs, 24 hrs, 48 hrs, or 168 hrs after the final treatment. Urine and feces from the last of these groups were taken for analyses at intervals to assess possible change in patterns over repeat dosing. Females gave no indication of changes in urinary label excreted per day over the period. Males appeared to increase urinary label output from the first to the second 24-hr collection before steady state was evident. Total urinary output averaged 82% and 88% of administered dose (AD) in M and F, respectively. Fecal outputs were 19% and 10% of AD, respectively (suggesting that females absorb and clear a.i. more quickly than males). There was no systematic change in organ/tissue concentrations within genders comparing 6 hrs after either 1, 4, or 7 consecutive doses. Tissue levels were generally higher in males than in females at comparable treatment times. Reductions in radiolabel in excreta and in tissues were rapid after cessation of dosing, irrespective of single or multiple dosing history in either sex. Study is adequate for its purpose. Aldous, July 2, 2010.

53099-0011 249691 Lauck-Birkel, S., “U-¹⁴C-phenyl-AE F115008: Rat metabolism - repeated oral dose (7 x 100 mg/kg body weight),” Hoechst Schering AgrEvo GmbH, Frankfurt, Germany, 7/31/98. Study ID: CM97/031, Hoechst # C 000362. Using urine and fecal extracts from study 53099-0011 249690, the investigator evaluated the major metabolites at 0-24 hrs after the first dose and 0-96 hrs after the last dose. A comparison of % administered dose (AD) found no substantive sex-related differences associated with a 7-day dosing history for urinary or fecal metabolite patterns within either sex. Following single and repeated oral administration, the same metabolites were found in comparable ratios in excreta. As found in other studies, a larger portion of radiolabel was found in females than in males, and females had a larger proportion of AD as parent a.i. than did males. Study is adequate for its purpose. Aldous, Nov. 3, 2010.

53099-0011 249692 Lauck-Birkel, S., “U-¹⁴C-phenyl-AE F115008: Dog metabolism - oral high (200 mg/kg body weight) and low dose (6 mg/kg body weight),” Hoechst Schering AgrEvo GmbH, Frankfurt, Germany, 6/15/98. Laboratory Study # CM96/062, Hoechst # A 67649. Samples derived from Study TEP204/8, involving 2 male dogs/group, sampled at intervals up to 72 hrs for urine and feces and up to 24 hrs for plasma. Disposition in dogs was similar to that in rats: rapid absorption, rapid excretion, with urine containing most of the label, and parent AE F115 008 the dominant moiety. Identified metabolites were generally the common metabolites of rat studies (see Record Nos. 249682 or 249684). Total urinary excretion was 72% and 69% of administered dose (AD) in high and low dose dogs, respectively. Corresponding 72 hr fecal excretion was 22% and 23%. Parent AE F115 008 collected within the first 48 hrs constituted 61% and 54% of AD in urine of high and low dose dogs. Corresponding fecal excretion of AE F115008 was 11% and 8% of AD. Major urinary metabolites in high dose dogs were AE F145740 (3.49% of AD), AE F143133 (2.17% of AD), AE F075736 (0.58% of AD), and AE F145741 (0.37% of AD). Urine of low dose dogs had slightly smaller amounts of these metabolites. Most of these metabolites were also found in feces. One metabolite observed only in urine was AE F143628 (detectable only in low dose dogs at 0.27% of AD): methyl 4-iodo-2-

ureidosulfonyl-benzoate. Parent AE F115 008 was the dominant labeled plasma component. Useful supplementary data. Aldous, Nov. 3, 2010.

53099-0012 249693 “Dermal Absorption in the Rat,” Covance North Yorkshire, England, 10/28/1998. This study type is reviewed by DPR Worker Health and Safety Group.

SUBCHRONIC AND SUBACUTE STUDIES

**53099-0002 249642 Wason, S. M., “Hoe 115 008, 93.3% w/w, Code: Hoe 115008 00 ZC93 0001, rat 90-day dietary repeat dose study with 4 week regression,” AgrEvo UK Ltd., Essex, England, 6/19/97. Laboratory Study #: Tox 94239. Groups of ten (CrI:COBS CD (SD) BR) rats /sex/group were dosed in diet with Iodosulfuron-Methyl-Sodium Technical (named Hoe 115 008), 93.8% purity, for 13 weeks in a subchronic study. The main study involved dose levels of 0, 200, 1000, 5000, or 10000 ppm. Recovery groups of 10/sex/group were similarly treated, but taken off treatment for 4 weeks prior to evaluation of blood for hematology and clinical chemistry, and to necropsy and histopathology. Achieved dose levels in treated males were 13.8, 67, 347, and 686 mg/kg/day for 200 through 10000 ppm groups respectively. Corresponding females received 15.4, 74, 388, and 790 mg/kg/day, respectively. NOEL = 1000 ppm in both sexes, based on body weight decrements. At termination of the main study, 5000 ppm and 10000 ppm males weighed 9% and 13% less than controls. Decrement in corresponding females were 9% and 11%. Food consumption tended to be reduced at 10000 ppm in both sexes. Modest reductions in RBC counts and hemoglobin values in 10000 ppm males and females suggest treatment-related decrements in both sexes. Reduced hematocrits in 10000 ppm females are likely treatment-related. Histopathology in main study groups revealed “slight” hypertrophy of centrilobular hepatocytes of 5/10 high dose males as the only noteworthy finding. Study is acceptable, with no adverse effects. Aldous, Nov. 3, 2010.

NOTE: Record No. 249643 in Part 2 of this report is the diet analysis.

53099-0002 249644 Wason, S. M., “Hoe 115 008, 93.3% w/w, Code: Hoe 115 008 00 ZC93 0001, mouse 90-day dietary repeat dose study,” AgrEvo UK Ltd., Essex, England, 6/19/97. Laboratory Study # Tox 94236. Groups of ten (CrI:CD-1 (ICR) BR) mice/sex/group were dosed in diet with Iodosulfuron-Methyl-Sodium Technical (named Hoe 115 008), 93.8% purity, for 13 weeks in a subchronic study at dose levels of 0, 700, 2100, or 7000 ppm. Achieved dose levels in treated males were 119, 332, and 1311 mg/kg/day for 700 through 7000 ppm groups respectively. Corresponding females received 139, 401, and 1332 mg/kg/day, respectively. NOEL < 700 ppm in males. NOEL = 700 ppm in females. Centrilobular hepatocellular enlargement was the most prominent finding, defining the NOEL’s. Lipofuscin granules were observed in centrilobular hepatocytes in 2100 to 7000 ppm males. Liver ORO staining found centrilobular fat deposits in 2100 to 7000 ppm males. Liver weights were significantly elevated in 2100 to 7000 ppm males and in 7000 ppm females. Body weights were reduced in 7000 ppm males. **Acceptable, with no adverse effects. Aldous, July 2, 2010.

NOTE: Record No. 249645 in Part 2 of this report is the diet analysis.

**53099-0003 249646 Wason, S. M., “Hoe 115 008 (AE F115008) technical substance, Code: Hoe 115 008 00ZC93 0001, dog 90-day oral (dietary) toxicity study,” AgrEvo UK Ltd., Essex,

England, 7/14/98. Study ID: Tox 94465, Report # Tox/95/246-8. Groups of 4 beagles/sex/group were dosed in diet with Iodosulfuron-methyl-sodium Technical (Hoe 115008), 88.7% purity, for at least 91 days in a subchronic study at 0, 200, 1200, or 7200 ppm. Achieved dose levels were 8.1, 49, and 301 mg/kg/day (M), and 8.4, 51, and 317 mg/kg/day (F). NOEL = 200 ppm. One 1200 ppm female had extramedullary hematopoiesis of the spleen and splenic enlargement, both of which were characteristic of high dose dogs of either sex, particularly for the 3 humane sacrifice dogs. A consistent reduction in eosinophil count (usually statistically significant) was observed at 1200 ppm in both sexes. Since eosinophil counts were much further reduced at 7200 ppm, a mid-dose treatment response is plausible. Small decrements in RBC parameters at 1200 ppm (RBC count, Hb, HCT) were equivocal indications of treatment effects. The highest dose was excessive. One male and 2 females were sacrificed moribund at 7200 ppm. Survivors had low body weights and/or had "wasted" appearance. There were profound decrements in RBC parameters at 7200 ppm (RBC count, Hb, HCT). Other anemia indications were extramedullary hematopoiesis of spleen, liver, and joints. A differential analysis of bone marrow contents showed a relatively greater progression toward the granulocytic series rather than precursors of RBC's. One dog per sex had "very severe" degree bronchopneumonia. In the affected female, Streptococci were present, some of which were hemolytic. Severe chronic pleuritis was observed in another high dose female. Liver findings unique to high dose dogs were slight centrilobular congestion and pigmented Kupffer cells, each present in two high dose dogs. Palpebral follicular conjunctivitis was observed in 3/sex high dose dogs, and not in other groups. **Acceptable, with no adverse effects.** Aldous, 9/23/10.

53099-0013 249850 Wason, S. M., "Hoe 115 008 (AE F115008) technical substance, Code: Hoe 115 008 00ZC93 0001, dog 28-day dietary range-finding study," AgrEvo UK Ltd., Essex, England, 8/20/98. Study ID: Tox 94463, Report # Tox/95/246-6. Groups of 2 beagles/sex/group were dosed in diet with Iodosulfuron-methyl-sodium Technical (Hoe 115008), 93.8% purity, for 28 days in a subacute study at 0, 800, 2400, 7200, or 20000 (reduced to 15000 on day 13) ppm. Achieved dose levels were 39, 122, 373, and 488 mg/kg/day (M), and 41, 119, 383, and 560 mg/kg/day (F). NOEL = 2400 ppm. The highest dose was clearly excessive: food consumption was reduced by 40% to 50%; mean body weight was reduced 1-2 kg compared to other groups; reduced activity and unsteady gait was observed in one female, "wasted" condition was observed in 1/sex, soiling of body or hair was observed in 3 dogs, both males were coughing near end of treatment, eyes of all 4 dogs had conjunctivitis; relative liver weights were markedly increased; RBC counts, Hb levels, and HCT were moderately reduced; mucosal erosion of gastric epithelium was observed in 3 dogs; and one male had very high neutrophil count and a very high erythrocyte sedimentation rate (ESR), suggesting infection. The other high dose male also had high ESR, suggesting inflammatory response. Bronchopneumonia was observed in 3/4 high dose dogs. Common findings at 7200 ppm included anal soiling at termination in one male (with occult blood); depressed RBC parameters; and increased liver relative weights. 53099-0013 249851 is the dietary concentration analysis for Record No. 249850. At the end of this report is a summary of stifle joint findings (assigned Record No. 249852), which reported slight to moderate hematopoietic hyperplasia in all 7200 ppm dogs, and in the 2 technically-readable high dose dogs (consistent with hematological findings as characteristic toxicity). Useful supplementary data, supporting dose selection for the 3-month dog study. No DPR worksheet for this report. Aldous, 9/14/10.

SUPPLEMENTARY STUDIES: NOT ON THE ACTIVE INGREDIENT:**GENE MUTATION STUDIES ON IODOSULFURON-METHYL-SODIUM METABOLITES**

53099-0009 249668 Stammberger, I. and K. Braun, "AE F059411; substance, technical, (Code AE F059411 00 1C99 0001): Bacterial reverse mutation test," Hoechst AG, Frankfurt, Germany, 9/15/98. Test article was 2-amino-4-methoxy-6-methyl-1,3,5-triazine, an inferred intermediate in the metabolism scheme between two minor metabolites (article is designated as HOE 059411 in metabolism studies such as Record No. 249682). Article was of low toxicity and was not mutagenic. No DPR worksheet is needed for this supplementary study. Aldous, 5/28/10.

53099-0009 249669 Stammberger, I. and K. Braun, "Bacterial reverse mutation test: AE C627337; substance, technical, Code AE C627337 00 1C90 0001," Hoechst AG, Frankfurt, Germany, Dec. 2, 1998. Test article was methyl 4-iodo-2-ureidosulfonyl-benzoate (the a.i. without the 1,3,5-triazine). This is a possible metabolite of the a.i., but not displayed in metabolism study schemes such as Record No. 249682. Article was of low toxicity and was not mutagenic. No DPR worksheet is needed for this supplementary study. Aldous, 5/28/10.

53099-0009 249670 Stammberger, I. and K. Braun, "AE F114844; substance, technical, (Code AE F114844 00 1C97 0001 : Bacterial reverse mutation test," Hoechst AG, Frankfurt, Germany, 10/15/98. Test article was methyl 4-iodo-2-[3-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)ureidosulfonyl]-benzoate. Chemical name is identical with the a.i. except that the a.i. specifies sodium salt. This test article has a different code from the technical a.i., and slightly different color and purity. Article was of toxicity similar to that of the a.i. technical, and was not mutagenic. No DPR worksheet is needed for this supplementary study. Aldous, 6/24/10.

53099-0009 249671 Stammberger, I. and K. Braun, "AE F114368; substance, technical, (Code AE F114368 00 1C99 0001 : Bacterial reverse mutation test," Hoechst AG, Frankfurt, Germany, Sept. 7, 1998. Test article was methyl 4-iodo-2-aminosulfonyl-4-benzoate. This is a minor metabolite of the a.i., displayed in metabolism study schemes such as Record No. 249682. Article was of low toxicity and was not mutagenic. No DPR worksheet is needed for this supplementary study. Aldous, 5/28/10.

53099-0009 249672 Stammberger, I. and K. Braun, "AE F113133; substance, technical, (Code AE F113133 00 1C98 0001 : Bacterial reverse mutation test," Hoechst AG, Frankfurt, Germany, 10/29/98. Test article was methyl 6-iodo-1,2-benzothiazol-3(2H)-one 1,1-dioxide. This is a minor metabolite of the a.i., displayed in metabolism study schemes such as Record No. 249682. Article was of low toxicity and was not mutagenic. No DPR worksheet is needed for this supplementary study. Aldous, 5/28/10.

53099-0009 249673 Stammberger, I. and K. Braun, "Bacterial reverse mutation test: AE C627339; substance, technical, Code AE C627339 00 1C97 0001," Hoechst AG, Frankfurt, Germany, Dec. 2, 1998. Test article was 2,2'-[carbonylbis(iminosulfonyl)]-bis(4-iodobenzoic acid) dimethyl ester. This is apparently a minor component of the a.i. or metabolite of the a.i. Article was of low toxicity and was not mutagenic. No DPR worksheet is needed for this supplementary study. Aldous, 5/28/10.