CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Imazosulfuron

Chemical Code # 5987, **Tolerance #** 53068
SB 950 # NA

1/14/10

I. DATA GAP STATUS

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

Toxicology one-liners are attached.

All record numbers through #249226 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T100114
Revised by T. Moore, 1/14/10

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

COMBINED, RAT

**** 0012, 241223**; "A Combined Chronic (24 Months) Oral Toxicity and Oncogenicity Study with TH-913 in the Rat Via Dietary Admixture" (Atkinson, J.E., Bio/dynamics, Inc., East Millstone, NJ, Laboratory Project Identification: 88-3257, 11/19/1991). 870.4300. TH-913 (multiple lot numbers (purity) of 11263211 (99.8%), 50031740 (99.7%), 50033340 (99.6%), 50035240 (99.6%), and 500037940 (99.6%)) was admixed to the diet and fed to 80 CD (Sprague-Dawley derived) rats per sex per dose at dose levels of 0, 200, 2000, or 20000 ppm (0, 10.39, 106.10, and 1123.99 mg/kg/day, respectively, for males and 0, 12.94, 132.46, and 1554.35 mg/kg/day, respectively, for females) for 24 months with 10 animals per sex per dose scheduled for interim sacrifice at 6 months, 12 months, and 18 months. Mortality totals (for main group animals found dead or killed in a moribund condition) after 24 months were as follows (0, 20, 2000, 20000 ppm)- males: 32/50, 33/50, 34/50, 25/50, respectively; females: 35/50, 28/50, 27/50, 42/50, respectively). A treatment-related decrease in mean body weight was observed in both sexes at 20000 ppm throughout the study. Treatment-related decreases in mean corpuscular volume and mean corpuscular hemoglobin concentration levels were observed in males at termination and, occasionally in females, at 20000 ppm; treatment-related decreases in mean hemoglobin and mean hematocrit levels in females were observed at 20000 ppm at 3 months, 12 months, and early termination. Dose-related increases in the mean relative weight of several organs including brain, liver, kidneys, and adrenals were observed in both sexes throughout the study; however, no treatment-related histopathological findings were observed in these organs. Examination of the eyes revealed treatment-related retinal degeneration and posterior subcapsular or complete cataracts at 20000 ppm in males at termination (24 months) and in females at 6 months (cataracts only), 12 months, and 18 months. Microscopic examination revealed bilateral retinal atrophy in both sexes at 20000 ppm and bilateral lens cataracts in females at 20000 ppm. Histopathological examination revealed no treatment-related neoplasms. **Possible adverse effects: retinal atrophy and cataracts.** NOEL (M) = 106.10 mg/kg/day (2000 ppm) and NOEL (F) = 132.46 mg/kg/day (2000 ppm) based on a decrease in body weight gain and on the presence of retinal atrophy and cataracts. **Acceptable**. (Corlett and Leung, 10/08/2009)

CHRONIC TOXICITY, RAT

See Combined, Rat above.

CHRONIC TOXICITY, DOG

** 0011; 241222; "One Year Oral Toxicity Study in Dogs with TH-913" (Spicer, E. J. F.,International Research and Development Corporation, Mattawan, MI, IRDC Study No. 295-119, 09/01/1992). 870.4100. TH-913 Technical (Lot Nos. 50031740 and 50035240 with purity = 99.7% and 99.6%, respectively) was administered orally by gelatin capsules to 4 beagle dogs per sex per dose at dose levels of 0 (empty gelatin capsules), 75, 150, and 300 mg/kg/day for 1 year. One male and one female at 300 mg/kg/day died during the study. No treatment-related clinical signs were observed. No treatment-related effect on body weight or food consumption was observed. An increase in mean relative liver weight was observed in both sexes at 150 and 300 mg/kg/day and a treatment-related increase in mean relative thyroid weight was observed in males at 300 mg/kg/day. Microscopic examination revealed a treatment-related hypertrophy of the thyroid in both sexes at 150 and 300 mg/kg/day. **No adverse effects.** NOEL (M/F) = 75 mg/kg/day based on hypertrophy of the thyroid. **Acceptable.** (Corlett, 04/21/2009)

ONCOGENICITY, RAT

See Combined, Rat above.

ONCOGENICITY, MOUSE

** 0013, 241224; "An Eighteen Month Oncogenicity Study with TH-913 in the Mouse Via Dietary Admixture" (Atkinson, J.E., Bio/dynamics, Inc., East Millstone, NJ, Laboratory Project Identification: 88-3258, TFT-0058, 03/31/1991). 870.4200. TH-913 (multiple lot numbers (purity) of 11263211 (99.8%), 50031740 (99.7%), 50033340 (99.6%), 50035240 (99.6%), and 500037940 (99.6%)) was admixed to the diet and fed to 50 CD-1 mice per sex per dose at dose levels of 0, 450, 4500, or 45000 ppm (0, 72.7, 741.3, and 7848.1 mg/kg/day, respectively, for males and 0, 86.8, 870.0, and 10303.5 mg/kg/day, respectively, for females) for 550 to 557 days (depending on the day of sacrifice). Mortality totals (for animals found dead or killed in moribund condition) were as follows (0, 450, 4500, 45000 ppm)- males: 18/50, 27/50, 22/50, 26/50, respectively; females: 18/50, 21/50, 23/50, 20/50, respectively). A treatment-related decrease in mean body weight gain was observed in both sexes at 45000 ppm throughout the study. A treatment increase in the mean relative liver weight was observed in both sexes at 45000 ppm. Microscopic examination revealed treatment-related centrilobular swelling of hepatocytes in both sexes at 45000 ppm. Histopathological examination revealed no treatment-related neoplasms. **No adverse effects.** NOEL (M) = 741.3 mg/kg/day (4500 ppm) and NOEL (F) = 870.0 mg/kg/day (4500 ppm) based on a decrease in body weight gain, an increase in mean relative liver weight, and centrilobular swelling of hepatocytes. **Acceptable**. (Corlett and Leung, 10/26/2009)

REPRODUCTION, RAT

** 0011, 241221; "Two Generation Reproduction Study in Rats with TH-913" (Schardein, J.L., International Research and Development Corporation, Mattawan, MI, Study No. 295-128, 12/19/1990). 870.3800. 26 males and 26 female Crl:CD VAF/Plus rats were administered TH-913 Technical (Lot No. 50035240, purity = 99.6%) in the diet at dose levels of 0 (diet only), 100, 1000, and 10000 ppm (0, 5.5-10.1, 56.5-102.9, and 590.6-926.9 mg/kg/day, respectively, for F0 males prior to mating, 0, 7.2-11.4, 69.4-106.8, and 678.3-982.5 mg/kg/day, respectively, for F0 females prior to mating, 0, 5.4, 53.9, and 581.6 mg/kg/day, respectively, for F0 females during gestation and 0, 15.1, 157.1 and 1279.0 mg/kg/day, respectively, for F0 females during lactation; 0, 5.8-13.1, 57.7-126.8, and 644.2-1384.0 mg/kg/day, respectively, for F1 males prior to mating, 0, 7.2-12.6, 69.8-129.7, and 799.3-1526.2 mg/kg/day, respectively, for F1 females prior to mating, 0, 5.6, 56.5, and 634.2 mg/kg/day, respectively, for F1 females during gestation and 0, 16.3, 158.5 and 1395.3 mg/kg/day, respectively, for F1 females during lactation). The premating period was 56 days from the start of the study for the F0 parents and 58 days from the selection for the F1 generation parents. Treatment continued through mating, gestation, and lactation. The litters were weaned at day 22 *post partum*. Treatment-related mortality in the F0 and F1 parents was observed at 10000 ppm. A treatment-related increase in scabbed areas around the head and shoulder region of the parents was observed at 10000 ppm. Treatment-related decreases in mean body weight and mean food consumption were observed in both sexes in the premating F0 and F1 parents at 10000 ppm. Treatment-related decreases in mean body weight and mean food consumption during gestation and lactation were observed in both F0 and F1 dams. Gross necropsy revealed no treatment-related findings in the F0 and F1 parents. Microscopic examination of the F0 and F1 parents (males and females) revealed no treatment-related abnormalities. A treatment-related decrease in mean live litter size in both F0 and F1 generations was observed at 10000 ppm. Treatment-related decreases in F1 mean pup weight at day 0 and in both the F1 and F2 pup weight at day 21 were observed at 10000 ppm. **No adverse effects. Parental NOEL (M)** (prior to mating) = 56.5-126.8 mg/kg/day (1000 ppm), **Parental NOEL (F)** (prior to mating) = 69.4-129.7 mg/kg/day (1000 ppm), both based on decreased mean body weight and food consumption; **Reproductive NOEL** = 53.9-56.5 mg/kg/day (1000 ppm), based on a decrease in mean live litter weight; **Offspring NOEL** = 157.1-158.5 mg/kg/day based on a decrease in mean pup weight. **Acceptable.** (Corlett and Leung, 06/19/09)

0011; 241220; "Reproduction Range-Finding Study in Mated Rats with TH-913" (Schardein, J.L., International Research and Development Corporation, Mattawan, MI, Study No. 295-116, 06/26/1989). TH-913 Technical (Lot No. 50031740, purity = 99.7%) was administered in the diet to 5 Charles River COBS CD rats per sex per dose at dose levels 0 (basal laboratory diet), 5000, 10000, 20000, 40000, or 80000 ppm (0, 282.2-324.1, 580.0-638.8, 1119.1-1123.7, 1992.2-2215.8, and 3340.0-4962.0 mg/kg/day, respectively, for males prior to mating, 0, 310.9-322.4, 606.8-643.9, 1095.6-1130.9, 1425.1-2117.6, and 1740.4-3089.0 mg/kg/day, respectively, for

females prior to mating, 0, 272.5, 526.2, 1082.7, 2785.3, and N/A mg/kg/day, respectively, for females during gestation and 0, 482.8, 1012.8, 1671.5, 2479.0, and N/A mg/kg/day, respectively, for females during lactation) starting 14 days before mating and ending after the mating period (males) or on lactation day 4 (females). Each female was cohabited with one male until evidence of mating was detected. Sacrificed *in extremis*/died- males: 0/5, 0/5, 0/5, 0/5, 1/5, 0/5, respectively; females: 0/5, 0/5, 0/5, 0/5, 1/5, 4/5, respectively. Treatment-related localized swelling (primarily of the limbs) was observed in 1 female at 40000 ppm and in 1 and 4 males at 40000 and 80000 ppm, respectively. Treatment-related decreases in mean body weights were observed in both males and females at dose levels of 20000 ppm and higher prior to mating. A treatment-related decrease in mean maternal body weight was observed at 40000 and 80000 ppm during gestation. Treatment-related decreases in mean food consumption were observed in males at dose levels of 20000 ppm and higher and in females at dose levels of 40000 ppm and higher prior to mating. A treatment-related decrease in mean maternal food consumption was observed at 80000 ppm during gestation. No mating and fertility effects were observed in animals treated with dose levels up to 40000 ppm and no effect on offspring viability was observed at dose levels up to 20000 ppm. At 40000 ppm, the only litter produced 4 dead pups all of which had morphological malformations. **Reported Parental NOEL (M)** (prior to mating) = 580.0-638.8 mg/kg/day (10000 ppm), **Reported Parental NOEL (F)** (prior to mating) = 606.8-643.9 mg/kg/day (10000 ppm), both based on decreased body weight; **Offspring NOEL** not determined due to lack of fetal data. **Supplemental study** (because only 5 animals per sex per dose group were used, because of a lack of fetal data, because the total number of homogenization-resistant spermatids and cauda epididymal sperm reserves were not enumerated, and because the study was ceased after one generation). (Corlett and Leung, 06/01/2009)

TERATOLOGY, RAT

** 0010, 241217; “Teratology Study in Rats with TH-913” (Schardein, J. L., International Research and Development Corporation, Mattawan, MI, Study No. 295-112, 06/07/1991). 870.3700. TH-913 Technical (Lot Nos. 50031740 and 50035240 with purities of 99.7% and 99.6%, respectively), suspended in 0.5% carboxymethylcellulose, was administered as a single daily dose by gavage to 25 mated female Sprague Dawley-derived Charles River COBS CD rats per dose at dose levels 0 (vehicle only), 0 (vehicle only), 250, 500, 1000, or 1500 mg/kg/day on days 6 through 15 of gestation. No maternal deaths were observed. No treatment-related clinical signs were observed. Treatment-related decreases in maternal mean body weight gain and food consumption were observed at 1500 mg/kg/day during the first interval of treatment (days 6 to 9). Macroscopic examination of the dams revealed no treatment-related changes. No treatment-related effects on fetus viability, posimplantation loss, placental and fetal body weights, and fetal sex distribution ratio were observed. No treatment-related fetal malformations or developmental variations were observed. **No adverse effects indicated. Reported Maternal NOEL** = 1000 mg/kg/day (based on decreased weight gain and food consumption during the first interval of treatment), **Developmental NOEL** = 1500 mg/kg/day (based on no effects at the highest dose tested). **Acceptable.** (Corlett and Leung, 05/13/2009)

0010; 241216; “Range-Finding Teratology Study in Rats with TH-913” (Schardein, J.L., International Research and Development Corporation, Mattawan, MI, Study No. 295-111, 05/12/1989). TH-913 Technical (Lot No. 50031740, purity = 99.7%) was administered as a single daily dose by gavage to 5 mated female Charles River COBS CD rats per dose at dose levels 0 (0.5% carboxymethylcellulose only), 500, 1000, 2000, 4000, or 6000 mg/kg/day on gestation days 6 through 15. Sacrificed *in extremis*/died: 0/5, 0/5, 0/5, 4/5, 5/5, respectively. One animal at 2000 mg/kg/day and the surviving animal at 4000 mg/kg/day appeared emaciated throughout the study interval. Necropsy on the animals that were sacrificed *in extremis* or died revealed erosions or foci in the glandular mucosa of the stomach. Treatment-related decreases in mean body weight gain and food consumption were observed at dose levels of 1000 mg/kg/day and higher; mean food consumption in surviving animals returned to mean control group levels by gestation day 16. **Reported Maternal NOEL** = 500 mg/kg/day (based on decreased weight gain and food consumption), **Developmental NOEL** not determined due to missing individual fetal

data. **Supplemental study** (only 5 animals per sex per dose group were used and because the fetuses were not weighed, not examined for external anomalies, and not examined for skeletal and soft tissue anomalies). (Corlett, 05/01/2009)

TERATOLOGY, RABBIT

** 0011, 0032; 241218, 249226; "Developmental Toxicity Study in New Zealand White Rabbits with TH-913" (Lamphear, C.K., International Research and Development Corporation, Mattawan, MI, Study No. 295-124, 10/28/1991, amended 08/06/2008). 870.3700. TH-913 Technical (Lot No. 50035240, purity = 99.6%), suspended in 0.5% carboxymethylcellulose, was administered as a single daily dose by gavage to 20 inseminated female New Zealand White rabbits per dose at dose levels 0 (vehicle only), 25, 50, or 125 mg/kg/day on days 7 through 19 of gestation. One animal at 125 mg/kg/day was sacrificed *in extremis* on gestation day 17; this animal had impaired function of the hindlimbs prior to sacrifice and necropsy on this animal revealed necrotic foci on the lungs. No other treatment-related deaths or clinical signs were observed. No effects on maternal mean body weight gain or food consumption was observed. No treatment-related effects on fetus viability, posimplantation loss, fetal body weights, and fetal sex distribution ratio were observed. No treatment-related fetal malformations or developmental variations were observed. **No adverse effects indicated. Reported Maternal NOEL** = 125 mg/kg/day (based on no effects at the highest dose tested), **Developmental NOEL** = 125 mg/kg/day (based on no effects at the highest dose tested). **Acceptable.** (Corlett and Leung, 10/13/2009)

0011; 241219; "Range-Finding Teratology Study in Rabbits with TH-913" (Schardein, J.L., International Research and Development Corporation, Mattawan, MI, Study No. 295-113, 08/25/1989). TH-913 Technical (Lot Nos. 50031740 and 50035240 with purities of 99.7% and 99.6%, respectively), suspended in 0.5% carboxymethylcellulose, was administered twice daily by gavage to 5 inseminated female New Zealand White rabbits per dose at dose levels 0 (vehicle only), 500, 1000, 2000, 4000, or 6000 mg/kg/day on gestation days 7 through 19 and as a single daily dose by gavage to 5 inseminated female New Zealand White rabbits per dose at dose levels 0 (vehicle only), 50, 100, and 250 mg/kg/day on gestation days 7 through 19. Sacrificed *in extremis*/died- dosed twice daily group: 3/5, 5/5, 5/5, 5/5, 5/5, respectively; dosed once daily group: 0/5, 0/5, 0/5, 0/5, respectively. Treatment-related decreases in mean body weight gain and food consumption were observed at dose levels of 500 mg/kg/day and higher. **Reported Maternal NOEL** = 250 mg/kg/day (based on decreased weight gain and food consumption), **Developmental NOEL** not determined due to missing individual fetal data. **Supplemental study** (only 5 animals per sex per dose group were used and the fetuses were not weighed, not examined for external anomalies, and not examined for skeletal and soft tissue anomalies). (Corlett and Leung, 05/18/2009)

GENE MUTATION

** 0014, 241225; "Bacterial Reverse Mutation Test of TH-913 Technical" (Ohtsuka, M., Medical Scientific Research Laboratory Co., Ltd., Saitama, Japan, Laboratory Project Identification: K01-0518, TFT-0006, 06/23/88). 870.5100. Duplicate cultures of *S. typhimurium* strains TA1535, TA1537, TA98, and TA100 and of *Escherichia coli* WP2 *uvrA* were exposed (direct plate incorporation method) to TH-913 technical, Lot No. 11263211, purity = 99.8%, in the presence and absence of S9 rat liver fraction, at 0 (DMSO), 313, 625, 1250, 2500, and 5000 ug/plate and incubated for 48 hours at 37 ± 1°C. Positive controls were functional. There was no treatment-related increase in mutation frequency. **No adverse effects indicated. Unacceptable but possibly upgradable** with the submission of a scientific justification why 2 and not 3 plates per dose level were used in this study. (Corlett and Leung, 06/24/09)

** 0014, 241237; "TH-913 Technical: Mutation at the Thymidine Kinase (*tk*) Locus of Mouse Lymphoma L5178Y Cells (MLA) Using the Microtitre Fluctuation Technique" (Fellows, M., Covance Laboratories Limited, Harrogate, North Yorkshire, England, Laboratory Project Identification 586/193 D5140, 07/02/1999). 870.5300. Duplicate cultures of the $TK^{+/-}$ mouse

lymphoma L5178Y cell line were treated with TH-913 Technical (batch number 11263211, purity = 99.5%), in the presence and absence of S-9 rat liver fraction, for 3 hours at concentrations ranging from 62.5 to 950 ug/ml in the first experiment and from 125 to 950 ug/ml in the second experiment. Positive controls were functional. No marked toxicity or increase in mutant frequency was observed at any dose level tested in either experiment in the presence or absence of S-9. Under the conditions employed in this study, the test article was not found to be mutagenic. **No adverse effects indicated. Acceptable.** (Corlett and Leung, 08/03/09)

CHROMOSOME EFFECTS

** 0014, 241238; "Chromosomal Aberration Test with TH-913 Technical" (Kajiwara, Y., Hita Research Laboratories, Chemical Biotesting Center, Chemicals Inspection & Testing Institute, Hita, Japan, Laboratory Project Identification K06-0073 TFT-0009, 09/19/1988). 870.5375.

Duplicate cultures of Chinese hamster lung fibroblasts were treated with TH-913 Technical (Lot No. 11263211, purity = 99.8%) for 24 and 48 hours (in the absence of metabolic activation) and for 6 hours (in the presence of metabolic activation) at concentrations of 0, 125, 250, and 500 µg/ml. Dividing cells were arrested at metaphase by treatment with colcemid 2 hours prior to the end of the incubation of the cells. An increase in chromatid breaks and chromatid exchanges were observed at 500 ug/ml in cells cultured without metabolic activation during both the first and second trials. Positive controls were functional. **Possible adverse effect indicated:** observed chromosome aberrations. **Acceptable**. (Corlett and Leung, 08/20/09)

DNA DAMAGE

** 0014, 241239; "Micronucleus Test on Imazosulfuron in CD-1 Mice" (Kitamoto, S., Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan, Laboratory Project Identification: 4011 TFT-0122, 03/26/2007). 870.5395. Imazosulfuron (Lot No. 52027641, purity = 98.6%) was prepared in 0.5% aqueous sodium carboxymethylcellulose and administered by gavage to groups of 5 Crlj:CD1 (ICR) male mice, one group treated with dose levels of 0 (vehicle only), 500, 1000, and 2000 mg/kg (treated for 24 hours), another group treated with dose levels of 0 (vehicle only) and 2000 mg/kg (treated for 48 hours with the death of one animal in the control group), and final group again treated with dose levels of 0 (vehicle group) and 2000 mg/kg (treated for 48 hours). Bone marrow cells from the femur were examined: polychromatic erythrocytes were evaluated for the presence of micronuclei and the ratio of polychromatic erythrocytes to normochromatic erythrocytes plus polychromatic erythrocytes was determined for each dose level. No treatment-related effects were observed. The positive control was functional. **No adverse effects indicated. Acceptable.** (Corlett and Leung, 08/27/2009)

NEUROTOXICITY

Rat Acute Neurotoxicity Studies

0015, 0025, 0026; 241242, 246556, 246557, 246558, 246559; "Acute Neurotoxicity of Imazosulfuron by Oral Gavage in Rats" (Toghill, A., Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Laboratory Project Identification: AR7546-REG CO06013r1, 05/24/2007). 870.62. Imazosulfuron TG (Batch reference 52027641, purity = 98.6%), prepared in 0.5% w/v aqueous carboxymethylcellulose, was administered in a single dose by gavage to 10 HsdRccHan:WIST rats per sex per dose at dose levels of 0 (vehicle only), 80, 400, and 2000 mg/kg. No mortalities occurred. During FOB assessments conducted 4 hours after dosing hours of treatment), treatment-related effects observed in both sexes at 2000 mg/kg included tip toe gait, piloerection, upward curvature of the spine, activity decrease, and splayed gait (males only) with all signs clearing in all animals by day 2. FOB assessments revealed no treatment-related effects on days 8 and 15. A treatment-related decrease in motor activity was observed in males at 2000 mg/kg 4 hours after dosing but not on days 8 and 15; motor activity assessments revealed no treatment-related effects in the females test animals on days 1, 8, and 15 . Macroscopic and microscopic examinations revealed no treatment-related abnormalities. **No**

adverse effects. NOEL (M/F) = 400 mg/kg (based on clinical signs observed during FOB 4 hours after treatment). **Acceptable**. (Corlett and Leung, 05/05/2009)

0014; 241241; "Preliminary Acute Neurotoxicity of Imazosulfuron in Rats" (Toghill, A., Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Laboratory Project Identification: AR7545-REG, 05/24/2007). Imazosulfuron Technical (Batch reference number 52027641, purity = 98.6%), prepared in 0.5% w/v aqueous carboxymethylcellulose, was administered in a single dose by gavage to 3 HsdRccHan:WIST rats per sex per dose at dose levels of 0 (vehicle only), 500, 1000, and 2000 mg/kg. No mortalities occurred. Detailed observations (limited functional observation battery) were performed at approximately hourly intervals on day 1 for 8 hours after dosing and least once per day until day 7 of the study. Clinical observations included decreased activity in 1 male and 2 females at 1000 mg/kg and in 2 males and 3 females at 2000 mg/kg, splayed gait in 2 males and 1 female at 2000 mg/kg, increased response to touch in 2 males at 500 mg/kg, in 1 male and 3 females at 1000 mg/kg, and in 2 females at 2000 mg/kg, tip toe gait in 2 females at 2000 mg/kg, and upward curvature of the spine in 2 females at 1000 mg/kg and in 1 male and 1 female at 2000 mg/kg. All clinical signs were observed during day 1 only. There were no treatment-related macroscopic findings at *post mortem* examination. Estimated time of peak effect was approximately 4 to 5 hours. NOEL (M) < 500 mg/kg, NOEL (F) = 500 mg/kg (based on clinical observations). **Supplemental study** (1. only 3 animals per sex per dose group were used, 2. no motor activity tests were conducted, and 3. no neuropathological examinations were conducted). (Corlett, 03/03/2009)

Rat Subchronic Neurotoxicity Study

0016, -0025, -0026; 241243, 246556, 246557, 246558, 246559; "90 Day Dietary Neurotoxicity Study of Imazosulfuron in Rats" (Toghill, A., Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Laboratory Project Identification: PR1358-REG, CO06014r2, TFT-0126, 06/25/2007). 870.6200. Imazosulfuron TG (Batch reference number 52027641, purity = 98.6%) was admixed to the diet and fed to 12 HsdRccHan:WIST rats per sex per dose at dose levels of 0 (diet only), 800, 2500, or 8000 ppm (0, 54.0, 169.2, and 571.3 mg/kg/day, respectively for males, and 0, 61.9, 200.8, and 655.3 mg/kg/day, respectively for females) for at least 90 consecutive days. No mortalities occurred. No dose-related, treatment-related clinical signs were observed. A treatment-related decrease in mean body weight when compared to the control group was observed in both sexes at 8000 ppm. FOB and motor activity assessments revealed no treatment-related effects. Neuropathological examination of the central and peripheral nervous system revealed no treatment-related abnormalities. **No adverse effects.** NOEL (M) = 169.2 mg/kg/day (2500 ppm) and NOEL (F) = 200.8 mg/kg/day (2500 ppm) based on a decrease in body weight. **Acceptable.** (Corlett and Leung, 05/05/2009)

SUBCHRONIC TOXICITY STUDIES

Rat 4-Week Dietary Toxicity Study

0014; 241240; "A 28-Day Preliminary Dietary Toxicity Study of Imazosulfuron in Rats" (Toghill, A., Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Laboratory Project Identification: KR1671-REG, CO05014r2, TFT-0120, 01/16/2007). Imazosulfuron Technical (Batch reference number 52027641, purity = 98.6%) was admixed to the diet and fed to 8 HsdRccHan:WIST rats per sex per dose at dose levels of 0 (diet only), 3000, 8000, or 15000 ppm (0, 268.0, 736.7, and 1325.0 mg/kg/day, respectively for males, and 0, 268.8, 693.4, and 1230.4 mg/kg/day, respectively for females). One female at 15000 ppm was sacrificed on day 9 due to extreme weight loss, thin appearance, and pinched in sides. No other clinical signs were reported. A treatment-related decrease in mean body weight gain was observed in males at 8000 and 15000 ppm and in females at all dose levels. Macroscopic examinations revealed no treatment-related abnormalities. NOEL (M) = 3000 mg/kg/day, NOEL (F) < 3000 mg/kg/kg (based on a decrease in mean body weight gain). **Supplemental study** (1) only 8 animals per sex per dose

group were used, 2) no hematology was performed, 3) no serum chemistry was performed, 4) no detailed clinical observations that included handling and observations outside the home cage in a standard arena were conducted, and 5) no histopathology was performed on the organs and tissues of the animals in the control and high dose groups). (Corlett, 03/12/2009)

Rat Subchronic Dietary Toxicity Study

0009; 241210; "A Subchronic (3 Months) Oral Toxicity Study with TH-913 in the Rat Via Dietary Admixture" (Barrett, D.S., Bio/dynamics, Inc., East Millstone, NJ, Laboratory Project Identification: 87-3244, 10/18/1990). 870.3100. TH-913 Technical (Lot No. 11263211, purity = 99.8%) was admixed to the diet and fed to 10 Charles River CD (Sprague-Dawley derived) rats per sex per dose at dose levels of 0 (diet only), 2500, 10000, or 45000 ppm (0, 234.7, 956.3, and 4577.2 mg/kg/day, respectively for males, and 0, 265.7, 1081.4, and 5135.7 mg/kg/day, respectively for females, values calculated by the reviewer) for 3 months. One male and two females at 45000 ppm died during the study. No treatment-related clinical signs were reported. A treatment-related decrease in mean body weight was observed in both sexes at 10000 and 45000 ppm. Decreases in mean corpuscular volume and mean corpuscular hemoglobin concentration levels were observed at 45000 ppm in both sexes. Decreases in mean serum total protein, globulin, and cholesterol levels were observed at 45000 ppm in both sexes. A treatment-related increase in mean relative liver weight was observed in both sexes at 45000 ppm. Microscopic examination revealed a treatment-related hypertrophy of the central lobular hepatocytes in both sexes at 45000 ppm. **No adverse effects.** NOEL (M) = 234.7 mg/kg/day (2500 ppm) and NOEL (F) = 265.7 mg/kg/day (2500 ppm) based on a decrease in body weight. **Acceptable.** (Corlett, 03/27/2009)

Rat 21-Day Repeated Dosing Dermal Toxicity Study

0010; 241214; "A 21-Day Repeated Dose Dermal Toxicity Study of Imazosulfuron in Rats" (Ohta, T., Panapharm Laboratories Co., Ltd., Kumamoto, Japan, Study Number P060142, 11/01/2006). 870.3200. Imazosulfuron TG (Lot Number 52027641, purity = 98.6%), moistened with purified water, was applied to the clipped dorsal region of 10 Crl:CD (SD) rats per sex per dose at dose levels of 0 (water only), 100, 300, or 1000 mg/kg/day for 6 hours daily for 21 days. No mortalities occurred. Cageside observations and detailed clinical observations revealed no clinical signs. Examination of body weight and food consumption data revealed no treatment-related effects. Hematology and serum chemistry revealed no treatment-related effects. No treatment-related effects on organ weights were observed. Microscopic and macroscopic examinations revealed no treatment-related abnormalities. **No adverse effects.** Reported NOEL (M/F, systemic) = 1000 mg/kg/day based on no effects at the highest dose tested; NOEL (M/F, skin) not determined since no skin irritation assessments were reported. **Supplemental study** (no detailed observations were performed outside the home cage in a standard arena and no assessments of motor activity, grip strength, and sensory reactivity to various stimuli were conducted). (Corlett, 04/10/2009)

Dog 4-Week Oral Toxicity Study

0010; 241212; "4 Week Oral Range-Finding Toxicity Study in Dogs with TH-913" (Spicer, E.J.F., International Research and Development Corporation, Mattawan, MI, IRDC Study 295-118, 05/23/1989). TH-913 Technical (Lot No. 50031740, purity = 99.7%) was administered orally by gelatin capsules to 2 beagle dogs per sex per dose at dose levels of 0 (empty gelatin capsules), 50, 100, 200, and 300 mg/kg/day for 4 weeks. No mortalities occurred. No treatment-related clinical signs were observed. Possible treatment-related decreases in mean body weight gain and food consumption were observed in both sexes at 300 mg/kg/day. Apparent increases in mean relative liver and thyroid/parathyroid weights were observed in females at 300 mg/kg/day. Macroscopic examinations revealed yellow/green kidneys and congested mesenteric lymph nodes in 1 male and 1 female at 300 mg/kg/day. NOEL (M) and (F) = 200 mg/kg/day (based on decreases in mean body weight gain and food consumption). **Supplemental study** (1) only 2 animals per sex per dose group were used, 2) the animals were treated for only 4 weeks, 3) no

hematology was performed, 4) no serum chemistry was performed, 5) no urinalysis was performed, and 6) no histopathology was performed on the organs and tissues of the animals in the control and high dose groups). (Corlett, 04/06/2009)

Mouse Subchronic Dietary Toxicity Study

0009; 241211; "A Subchronic (3 Months) Oral Toxicity Study with TH-913 in the Mouse Via Dietary Admixture" (Barrett, D.S., Bio/dynamics, Inc., East Millstone, NJ, Laboratory Project Identification: 87-3245, 11/20/1990). 870.3100. TH-913 Technical (Lot No. 11263211, purity = 99.8%) was admixed to the diet and fed to 10 CD-1 mice per sex per dose at dose levels of 0 (diet only), 2500, 10000, or 45000 ppm (0, 456.8, 1820.1, and 9776.5 mg/kg/day, respectively for males, and 0, 692.0, 2726.9, and 12695.2 mg/kg/day, respectively for females, values calculated by the reviewer) continuously for at least 90 days. No mortalities occurred. No dose-related clinical signs were reported. No treatment-related effects on body weight were observed. A treatment-related decrease in the mean red blood cell level in both sexes at 45000 ppm and a treatment-related decrease in the mean hemoglobin level in males at 45000 ppm were observed. Serum chemistry assays revealed no treatment-related effects. A treatment-related increase in the mean relative liver weight was observed in males at 10000 and 45000 ppm and in females at 45000 ppm. Microscopic examination revealed treatment-related hypertrophy of the central lobular hepatocytes in males at all dose levels and in females at 45000 ppm. **No adverse effects.** NOEL (M) < 456.8 mg/kg/day (2500) ppm and NOEL (F) = 2726.9 mg/kg/day (10000 ppm) based on hypertrophy of the central lobular hepatocytes. **Acceptable.** (Corlett, 04/02/2009)

METABOLISM STUDIES

0017; 241244; "Metabolism of Imazosulfuron in Rats (Pilot Study)" (Nagahori, H., Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan, Laboratory Project Identification: 4038, 03/28/2007). 870.7485. Two test articles were used in this study: 1. [im-^{14}C]imazosulfuon, lot no. CFQ14400, specific activity 2.15 Gbq/mmol, radiochemical purity> 99.0% together with unlabeled imazosulfuron, lot no. 52027641, purity = 98.6% and 2. [pm-^{14}C]imazosulfuon, lot no. CFQ14401, specific activity 2.04 Gbq/mmol, radiochemical purity> 98.6% together with unlabeled imazosulfuron, lot no. 52027641, purity = 98.6%, each of which was suspended in 0.5% carboxymethyl cellulose in ultrapure water and administered in a single dose by gavage to 1 Crl:CD (SD) rat per sex. ^{14}C excretion into the expired air was negligible. Fecal and urine samples were collected at 1, 2, and 3 days after the administration of the dosing compounds. For [im-^{14}C]imazosulfuon, 65.3% (male) and 69.0% (female) of radio-labeled dose was eliminated in the urine and 36.8% (male) and 31.8% (female) of the radio-labeled dose was eliminated in the feces 72 hours after dosing. For [pm-^{14}C]imazosulfuon, 64.4% (male) and 57.9% (female) of radio-labeled dose was eliminated in the urine and 37.2% (male) and 40.1% (female) of the radio-labeled dose was eliminated in the feces 72 hours after dosing. Both [im-^{14}C]imazosulfuon and [pm-^{14}C]imazosulfuon were extensively metabolized. For [im-^{14}C]imazosulfuon, metabolites HMS (54.6% of the dose in the male and 58.2% of the dose in the female) and IHDU (2.7% of the dose in the male and 4.3% of the dose in the female) were excreted in the urine 24 hours after dosing and metabolites HMS (6.9% of the dose in the male and 5.6% of the dose in the female), IHDU (0.8% of the dose in male and 0.3% of the dose in female), and ACIS (6.0% of the dose in the male and 4.3% of the dose in the female) were excreted in the feces 48 hours after dosing. For [pm-^{14}C]imazosulfuon, metabolites HMS (50.3% of the dose in the male and 47.8% of the dose in the female) and IHDU (5.1% of the dose in the male and 3.1% of the dose in the female) were excreted in the urine 24 hours after dosing and metabolites HMS (5.3% of the dose in the male and 13.4% of the dose in the female), IHDU (0.7% of the dose in the male and 0.5% of the dose in the female), and UK-1 (3.8% of the dose in the male and 4.0% of the dose in the female) were excreted in the feces 48 hours after dosing. From the identified metabolites, metabolic reactions were determined to be demethylation, hydroxylation of the pyrimidine ring, opening of the pyrimidine ring, and hydrolysis

of the sulfonylurea bridge. **Supplemental study** (only one male and one female were used for each test article). (Corlett and Leung, 11/03/09)

0017; 241245; "Metabolism of [imidazopyridinyl-3-^{14}C] Imazosulfuron in Male Rats (Tier 1 Study)" (Nagahori, H., Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan, Laboratory Project Identification: 4042, 05/31/2007). 870.7485. [im-^{14}C]imazosulfuron (lot no. CFQ14400, specific activity 2.15 Gbq/mmol, radiochemical purity> 99.0%) together with unlabeled imazosulfuron (lot no. 52027641, purity = 98.6%) was suspended in 0.5% carboxymethyl cellulose in ultrapure water and administered in a single dose by gavage to 4 male Crl:CD (SD) rats. Fecal and urine samples were collected at 6 and 12 hours (urine only), and 24, 48, and 72 days after the administration. 64.1% of radio-labeled dose was eliminated in the urine and 32.4% of the radio-labeled dose was eliminated in the feces 72 hours after dosing. The highest mean tissue concentrations of the radio-labeled dose were found in the carcass (0.15%), blood (0.04%), and liver (0.04%). [Imidazopyridinyl-3-^{14}C] Imazosulfuron was extensively metabolized. Metabolites HMS (55.7% of the dose), IHDU (4.1% of the dose), and HDS (1.9% of the dose) were excreted in the urine 48 hours after dosing. Metabolites HMS (6.5% of the dose), IHDU (0.4% of the dose), HDS (2.3% of the dose), IPSN (2.9% of the dose, from extracts 1 and 3), and ACIS (3.2% of the dose from extracts 1 and 3) were excreted in the feces 48 hours after dosing. From the identified metabolites, metabolic reactions were determined to be demethylation, hydroxylation, methylation of the hydroxyl group, opening of the pyrimidine ring, and hydrolysis of the sulfonylurea bridge. **Supplemental study** (no assessments of the test material concentrations in the bile of the test animals were conducted). (Corlett and Leung, 11/10/09)

0017; 241246; "Biliary Excretion of [imidazopyridinyl-3-^{14}C] Imazosulfuron in Male Rats (Tier 2 Study)" (Nagahori, H., Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan, Laboratory Project Identification: 4043, 07/31/2007). 870.7485. [Im-^{14}C]imazosulfuron (lot no. CFQ14400, specific activity 2.15 Gbq/mmol, radiochemical purity> 99.0%) together with unlabeled imazosulfuron (lot no. 52027641, purity = 98.6%) was suspended in 0.5% carboxymethyl cellulose in ultrapure water and administered in a single dose by gavage to 3 bile duct-cannulated male Crl:CD (SD) rats. Feces, bile, and urine samples were collected at 6 and 12 hours (urine and bile only), and 24, 48, and 72 days after the administration of the dosing material. 53.4% and 30.5% of the radio-labeled dose was eliminated in the urine and bile, respectively, 12 hours after dosing and 66.0%, 33.8%, and 1.9% of the radio-labeled dose was eliminated in the urine, bile, and feces, respectively, 24 hours after dosing. After 72 hours, 66.4%, 34.0%, 2.4%, and 0.3% of the of the radio-labeled dose had been found in the urine, bile, feces, and residual carcass, respectively. [Imidazopyridinyl-3-^{14}C] Imazosulfuron was extensively metabolized. Metabolites HMS (56.9% of the dose), IHDU (4.9% of the dose), and HDS (0.5% of the dose) were excreted in the urine 24 hours after dosing. Metabolites HMS (3.8% of the dose), IHDU-glu (5.2% of the dose), HDS (1.6% of the dose), and ACIS (1.1% of the dose) were excreted in the bile 24 hours after dosing. Metabolite HMS (0.8% of the dose) was excreted in the feces 24 hours after dosing. From the identified metabolites, metabolic reactions determined to have occurred were demethylation, hydroxylation of the pyrimidine ring, methylation or glucuronidation of hydroxyl group, and opening of the pyrimidine ring and formation of guanidine. **Acceptable.** (Corlett and Leung, 11/24/09)

STUDIES ON METABOLITES, PHOTOLYSIS PRODUCTS, AND INTERMEDIATES

Mutagenicity Studies

0014, 241226; "Bacterial Reverse Mutation Test of UDPM" (Ohtsuka, M., Hita Research Laboratories, Chemical Biotesting Center, Chemicals Inspection & Testing Institute, Hita, Japan, Laboratory Project Identification: T-2423, TFT-0051, 09/25/1990). 870.5100. Duplicate cultures

of *S. typhimurium* strains TA1535, TA1537, TA98, and TA100 and of *Escherichia coli* strain WP2 *uvrA* were exposed (direct plate incorporation method) to UDPM (TH-913 Photolysis Product), Lot No. 12361024, purity ≥ 99.0%, in the presence and absence of S9 rat liver fraction, at 0 (DMSO), 313, 625, 1250, 2500, and 5000 ug/plate and incubated for 48 hours at 37 ± 0.5°C. Positive controls were functional. There was no treatment-related increase in mutation frequency. **No adverse effects indicated. Supplemental study** (UDPM, is a photolysis product of the active ingredient TH-913). (Corlett and Leung, 07/01/09)

0014, 241227; "Bacterial Reverse Mutation Test of IHOA" (Ohtsuka, M., Hita Research Laboratories, Chemical Biotesting Center, Chemicals Inspection & Testing Institute, Hita, Japan, Laboratory Project Identification: TFT-0087, T92-1793, 03/26/1993). 870.5100. Duplicate cultures of *S. typhimurium* strains TA1535, TA1537, TA98, and TA100 and of *Escherichia coli* strain WP2 *uvrA* were exposed (pre-incubation method) to IHOA (a metabolite of imazosulfuron) (Lot No. 13109924, no purity information provided), in the presence and absence of S9 rat liver fraction, at 0 (purified water), 313, 625, 1250, 2500, and 5000 ug/plate, incubated in a test tube and shaken at 37 ± 0.5°C for 20 minutes, poured onto a minimal glucose agar plate, and incubated for 48 hours at 37 ± 0.5°C. Positive controls were functional. There was no treatment-related increase in mutation frequency. **No adverse effects indicated. Supplemental study** (IHOA is a metabolite of the active ingredient TH-913). (Corlett and Leung, 07/06/2009)

0014, 241229; "Bacterial Mutagenesis Study of M-1 (Metabolite of TH-913)" (Sakamoto, Y., Takeda Analytical Research Laboratories, Ltd., Osaka, Japan, Laboratory Project Identification: TFT-0031, 12/HC, 10/16/1989). 870.5100. In the bacterial reverse mutation test, duplicate cultures of *S. typhimurium* strains TA1535, TA1537, TA98, and TA100 and of *Escherichia coli* strain WP2 *uvrA* were exposed (pre-incubation method) to M-1 (a metabolite of TH-913) (Lot No. 11931729, purity = 100%), in the presence and absence of S9 rat liver fraction, at 0 (0.8% sodium carbonate solution), 156, 313, 625, 1250, 2500, and 5000 ug/plate, incubated in a test tube and shaken at 37°C for 20 minutes, poured onto a minimal glucose agar plate, and incubated for 72 hours at 37°C. Positive controls were functional. There was no treatment-related increase in mutation frequency. **No adverse effects indicated. Supplemental study** (M-1 is a metabolite of the active ingredient TH-913). (Corlett and Leung, 07/13/2009)

0014, 241229; "Bacterial Mutagenesis Study of M-1 (Metabolite of TH-913)" (Sakamoto, Y., Takeda Analytical Research Laboratories, Ltd., Osaka, Japan, Laboratory Project Identification: TFT-0031, 12/HC, 10/16/1989). 870.5500. In the bacterial DNA repair test, duplicate cultures of *Bacillus subtilis* strains H17 (rec^+) and M45 (rec^-) were treated with M-1 (a metabolite of TH-913) (Lot No. 11931729, purity = 100%), in the presence and absence of S9 rat liver fraction, at 0 (0.8% sodium carbonate solution), 156, 313, 625, 1250, 2500, and 5000 ug/disc for 18 to 20 hours at 37°C. Positive controls were functional. No zones of inhibition were observed in the treated cells. **No adverse effects indicated. Supplemental study** (M-1 is a metabolite of the active ingredient TH-913). (Corlett and Leung, 07/15/2009)

0014, 241234; "Bacterial Reverse Mutation Test of IPSN" (Ohtsuka, M., Hita Research Laboratories, Chemical Biotesting Center, Chemicals Inspection & Testing Institute, Hita, Japan, Laboratory Project Identification: K01-0592, TFT-0021, 12/05/1988). 870.5100. In the bacterial reverse mutation test, duplicate cultures of *S. typhimurium* strains TA1535, TA1537, TA98, and TA100 and of *Escherichia coli* strain WP2 *uvrA* were treated (plate incorporation method) with IPSN (an intermediate of TH-913) (Lot No. 1157940, purity = 99%), in the presence and absence of S9 rat liver fraction, at 0 (DMSO), 313, 625, 1250, 2500, and 5000 ug/plate and incubated for 48 hours at 37 ± 1°C. Positive controls were functional. There was no treatment-related increase in mutation frequency. **No adverse effects indicated. Supplemental study** (IPSN is an intermediate of TH-913). (Corlett and Leung, 07/20/2009)

0014, 241236; “Bacterial Reverse Mutation Test of ADPM” (Inai, T., Hita Research Laboratories, Chemical Biotesting Center, Chemicals Inspection & Testing Institute, Hita, Japan, Laboratory Project Identification: K01-0787, TFT-0044, 04/23/1990). 870.5100. In the bacterial reverse mutation test, duplicate cultures of *S. typhimurium* strains TA1535, TA1537, TA98, and TA100 and of *Escherichia coli* strain WP2 *uvrA* were treated (plate incorporation method) with ADPM (metabolite of TH-913) (Lot No. 7024, purity = 99.6%), in the presence and absence of S9 rat liver fraction, at 0 (DMSO), 313, 625, 1250, 2500, and 5000 ug/plate and incubated for 48 hours at 37 $\pm$ 0.5^{o}C. Positive controls were functional. There was no treatment-related increase in mutation frequency. **No adverse effects indicated. Supplemental study** (ADPM is a metabolite of the active ingredient TH-913). (Corlett and Leung, 07/21/2009)