

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
THIENCARBAZONE-METHYL

Chemical Code # 6016, Document Processing Number (DPN) # 53100
SB 950 # Not applicable
Original date: Dec. 10, 2010
Revised date: 7/12/11

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, possible 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:	No data gap, no adverse effect (rat acute and subchronic)

Toxicology one-liners are attached.

All record numbers for the above study types through 256725 (Document No. 53100-0078) were examined. This includes all relevant studies indexed by DPR as of 1/18/11.

In the 1-liners below:

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: t2011712.wpd

Revised by Name, Date: Aldous, Dec. 10, 2010 (original summary), Aldous, 7/12/11.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

COMBINED, RAT

**53100-0063 249805 Schladt, L., Chr. Rühl-Fehlert, and E. Hartmann, "BYH 18636: Combined chronic toxicity and carcinogenicity study in Wistar rats (dietary administration for 2 years)," Bayer Healthcare AG, Wuppertal, Germany, 1/30/07. Laboratory Study #: T3073715, Report No. AT03629. Groups of 60 rats/sex/group were dosed in diet with BYH 18636 (thiencarbazone-methyl), 96.0% purity, in the oncogenicity study at 0, 500, 2500, or 5000 ppm. Estimated achieved dose levels were 23, 115, and 234 mg/kg/day for increasing dose levels in males, and 30, 153, and 313 mg/kg/day in females. An additional 10/sex/group were allocated to a 1-yr chronic study, with dose levels of 0, 200, 500, 2500, or 5000 ppm. Protocol included FOB and motor activity and locomotor activity of chronic phase rats near to termination, in addition to standard parameters. NOEL = 5000 ppm in both sexes. There were no apparent treatment effects in either sex. Study is acceptable, with no adverse effects. Aldous, 6/30/10.

CHRONIC TOXICITY, RAT

(See COMBINED, RAT, above).

CHRONIC TOXICITY, DOG

53100-0062 249804 [subsequent report 53100-0078 256725, supplied missing histopathology data on females], Eigenberg, D. A., "A chronic toxicity feeding study in the beagle dog with Technical Grade BYH 18636," Bayer CropScience LP, Research Triangle Park, NC, Feb. 6, 2007 (amended). Laboratory Study # 05-C76-YO, Bayer Report No. 201497-1. Record No. 256725 was dated Dec. 10, 2010 and received by DPR on 12/21/10. Groups of 4 beagles/sex were dosed in diet with BYH 18636 (thiencarbazone-methyl), 96.4% purity in a chronic study. Initially the treated groups received 1000, 4000, or 8000 ppm for both sexes. Top dose was reduced to 7000 ppm for males and females at day 21 due to urinary calculi observed in 8000 ppm males. Calculi persisted in 3 of these males, therefore high dose males were taken off treatment for 4 days, with dose reduced to 6000 ppm from day 56 onward. Mean achieved dosages (accounting for high dose adjustments) were 29, 117, and 179 mg/kg/day for males and 27, 127, and 200 mg/kg/day for females. Study was initially designated unacceptable due to missing histopathology individual data for females. Record No. 256725 individual data for high dose females were examined to assess whether elevated eosinophil counts in 4000-8000 ppm females might be correlated with particular histopathology findings (no correlation evident). Study is now **acceptable, with **no adverse effects**. NOEL = 117 mg/kg/day for males based on urinary calculi, and 200 mg/kg/day for females (highest dose tested). Aldous, Dec. 10, 2010: re-examined by Aldous (after receipt of Record No. 256725) on 1/18/11.

ONCOGENICITY, RAT

(See COMBINED, RAT, above).

ONCOGENICITY, MOUSE

****53100-0064 249806** Wason, S., "Carcinogenicity study of BYH 18636 in the C57BL/6J mouse by dietary administration," Bayer CropScience, Sophia Antipolis, France, Nov. 10, 2006. Laboratory Study # SA 04062. Groups of 50 C57BL/6J mice/sex/group were dosed with BYH 18636 (thiencarbazone-methyl), 96.2% to 96.4% purity, in the oncogenicity study at 0, 200, 1000, or 4000 ppm. Estimated achieved dose levels were 29, 147, and 599 mg/kg/day in low to high dose males, and 37, 185, and 758 mg/kg/day in respective females. An additional 10/sex/group were allocated to 28-wk interim sacrifice groups to assess subchronic to chronic effects. NOEL = 1000 ppm. High dose males and females had urinary bladder stones (41/50 in males, 20/50 in females: comprised about 70-75% of test article), associated with urothelial hyperplasia, suburothelial mixed cell infiltrate, diffuse interstitial edema, intramuscular inflammatory cell infiltrate, and serosal mixed cell infiltrate. Bladder transitional cell papillomas were observed in 2 females and 1 male. Bladder transitional cell carcinoma occurred in one female. Urethral transitional cell carcinoma occurred in one male. These findings were generally unique to 4000 ppm mice (including the tumors), or occurred at the rate of no more than 1 in any group. In males, chronic ulcerative dermatitis (focal/multifocal) of a degree considered contributory to death was increased at 4000 ppm. The dermatitis, generally associated with "moderate" to "severe" cases of urinary bladder stone formation, was justifiably judged by investigators to be secondary to bladder stone irritation. The latter mortality/morbidity led to slightly elevated mortality in high dose males during the last 20 weeks of the study. Diffuse myeloid hyperplasia in sternal bone marrow was elevated in high dose males. This was highly correlated with chronic ulcerative dermatitis, and appears to be a secondary response. Kidney pelvic dilatation was elevated in both sexes, likely secondary to dysuria due to bladder stones. High dose males suffered modest (1-2 g) body weight decrements during most of the study. Thus all important findings, including tumors, appeared to derive from stone formation in urinary bladder lumen. Study is acceptable. Transitional cell tumors of urothelial epithelium are "possible adverse effects," elicited only at very high dosage with pre-disposing pathology. Aldous, Nov. 5, 2010.

REPRODUCTION, RAT

****53100-0061 249803** Eiben, R., "BYH 18636: Two-generation reproduction study in the Wistar rat by administration in the diet," Bayer Healthcare AG, Wuppertal, Germany, 7/18/06. Laboratory Study # T7063198. Wistar Crl: (WI) WU BR rats, 25/sex/group, were dosed in diet with BYH 18636 (thiencarbazone-methyl), 96.4% purity. Exposure was continuous over 10-wk pre-mating periods, throughout mating and lactation of one litter/generation at dose levels of 0, 500, 2500, and 10000 ppm, corresponding to mean pre-mating exposures of 46, 245, and 946 mg/kg/day in treated F0 males; 56, 264, and 968 mg/kg/day in F0 females; 50, 260, and 992 mg/kg/day in F1 males; 68, 353, and 1284 mg/kg/day in F1 females. Parental systemic toxicity NOEL = 2500 ppm (urolithiasis, particularly in kidneys; transitional cell hyperplasia; various inflammatory responses adjacent to urothelial epithelia; slightly reduced body weight and food consumption in females; and slightly elevated kidney weights in females). Parental reproductive effects NOEL = 10000 ppm (no effects observed). Offspring viability and growth NOEL = 10000 ppm (no treatment effects). Acceptable, with no adverse effects. Aldous, Oct. 11, 2010.

DEVELOPMENTAL TOXICITY, RAT

**53100-0059 249801 Langewische, F. W., "BYH 18636: developmental toxicity study in rats after oral administration," Bayer Healthcare AG, Wuppertal, Germany, 8/25/05. Laboratory Study # T4062961. Groups of 25 mated SPF Wistar dams/group were dosed with 0, 50, 200, or 1000 mg/kg/day thien carbazole-methyl (BYH 18636), 96.2% purity, in 10 ml/kg 0.5% aqueous CMC over gestation days 6-19 in a standard developmental toxicity study. Maternal NOEL = 200 mg/kg/day, based on significantly reduced food consumption and body weight, "light-colored feces" (which may represent color of test article), and sediment in urinary bladders of 12/20 high dose dams with viable offspring. Developmental toxicity NOEL = 200 mg/kg/day, based on 9% decrement in fetal terminal body weight and slight increases in wavy ribs and of ossification delays at 1000 mg/kg/day at several loci. Ossification delays were at sites in the developing skeleton where ossification is just appearing or actively progressing during late gestation, such as fifth metacarpal, fifth and sixth sternebrae, fourth sacral vertebral arches, and fourth to fifth caudal vertebral bodies. Developmental effects appear transitory, and do not indicate "possible adverse effects" considering the associated very high dose with maternal toxicity. Acceptable. Aldous, Aug. 6, 2010.

DEVELOPMENTAL TOXICITY, RABBIT

**53100-0060 249802 Wason, S., "BYH 18636: developmental toxicity study in the rabbit by gavage," Bayer CropScience, Sophia Antipolis, France, Jan. 6, 2006. Laboratory Study # SA 03350. Groups of 25 mated CrI:KBL(NZW) does were dosed with BYH 18636 (thien carbazole-methyl), 96.2% to 96.4% purity at 0, 50, 125, or 500 mg/kg/day during gestation days 6-28. Maternal NOEL = 50 mg/kg/day, based on yellow sediment in urine of 4 mid-dose does, and of all high dose does. High dose does had increased incidence of clinical signs such as "few feces" or "no feces." One of these does was sacrificed moribund. Since this individual had no signs of accidental trauma and did show clinical signs of diminished or absent feces prior to death, a relationship of a.i. exposure to morbidity is plausible. Food consumption was somewhat reduced at the high dose. Developmental NOEL = 125 mg/kg/day, based on slight reduction in fetal body weight. The study is acceptable, with no adverse effects. Aldous, 8/17/10.

GENE MUTATION

**53100-0065 249807 Herbold, B., "BYH 18636: Salmonella/microsome test: plate incorporation and preincubation method," Bayer Healthcare AG, Wuppertal, Germany, 1/25/07. Laboratory Study # T 4076830, Report AT03630. Test strains were *Salmonella typhimurium*: TA 1535, TA 100, TA 1537, TA 98, and TA 102. Initial test was plate incorporation, with preincubation for follow-up, with and without S-9. There were three replicates per step (at 2x intervals). None of the strains showed mutations with or without S-9. Toxicity, based on diminished revertants at the higher dose level(s), was variable between strains. TA 100 was the most robust strain, with toxicity evident only at about 240 µg/plate and above. TA 102 was the least tolerant strain, with toxicity evident at 32-60 µg/plate and above. Positive controls were functional. Acceptable, with no adverse effects. Aldous, 9/20/10.

53100-0065 249810 Wurnitzer, U., "BYH 18636: Salmonella/microsome test: plate incorporation and preincubation method," Bayer Healthcare AG, Wuppertal, Germany, Aug. 10, 2005. Laboratory Study # T 0073262, Report AT02274. Test system: *Salmonella typhimurium* strains TA 1535, TA 100, TA 1537, TA 98, and TA 102. Initial test was plate incorporation, with 3x steps between plate concentrations. Typically there were two complete additional trials with and without S-9 by pre-incubation for follow-up. There were three replicates per level in each trial. Toxicity, based on diminished revertants at the higher dose level(s), was variable between strains. TA 100 was the most robust strain, with 50% reductions in colonies at about 200 µg/plate. TA 102 was the least tolerant strain, with 50% reductions in colonies at about 50 µg/plate. **Not acceptable:** investigators often had difficulty providing more than two closely-spaced concentrations with treatments approaching toxic levels, yet with colony counts similar to controls. BYH 18636 produces bacteriostatic effects, starting at 30 µg/plate. Test material precipitated at 158 µg/plate and higher. Therefore, 500 µg/plate and higher could not be used for assessment. There were no remarkable increases in revertants. No adverse effects were identified. [Record No. 249807, subsequently conducted in the same facility, overcame problems occurring in this study, and is acceptable.] Aldous, 10/27/10.

**53100-0065 249813 Herbold, B., "BYH 18636: V79/HPRT-test *in vitro* for the detection of induced forward mutations," Bayer Healthcare AG, Wuppertal, Germany, 2/23/07. Laboratory Study # T6076832, Report AT03686. After 5 hrs exposure to test article [Thiencarbazone-methyl (BYH 18636), 94.6% purity], there were 6 days of subsequent incubation for phenotypic expression (with subculturing after about 3 days), and 6-8 days incubation for mutant selection (with 10 µg/ml 6-thioguanine). For non-activated and activated evaluations there were two flasks per concentration for each trial; two trials with and two without S-9. Aliquots from each flask were applied to eight 100 ml culture dishes in the mutant selection phase (3×10^5 cells per dish). Thiencarbazone-methyl concentrations were 30, 60, 120, 240, 360, 480, and 600 µg/ml. The highest two concentrations exceeded the solubility of a.i. in vehicle (DMSO), thus requiring sonication of a suspension in DMSO to add to treatment flasks. The a.i. was not cytotoxic at any concentration applied, and was negative for mutagenicity. Positive controls, [non-activated: EMS (900 µg/ml) or activated: DMBA (20 µg/ml)] were highly functional. Study is acceptable, with no adverse effects. Aldous, 9/21/10.

53100-0065 249814 Herbold, B., "BYH 18636: V79/HPRT-test *in vitro* for the detection of induced forward mutations," Bayer Healthcare AG, Wuppertal, Germany, 12/12/05. Laboratory Study # T1073263, Report AT02752. Procedure was essentially the same as Record No. 249813, above. Test article was Thiencarbazone-methyl (BYH 18636), 94.6% purity. Positive control treatment with EMS gave the expected strong response. DMBA treatment with S-9 activation gave only about five-fold increases in mutations over controls in 2 of 3 trials: a weak response, and probably why this study was repeated (Record No. 249813, above). One set of 600 µg/ml selection dishes was lost to contamination (non-S-9 system). This would not have compromised the study by itself. The a.i. was not cytotoxic at any treatment level, and was negative for mutagenicity. Useful supplementary data. No DPR worksheet. Aldous, 9/21/10.

CHROMOSOME EFFECTS

**53100-0066 249819 Thum, M., "BYH 18636: *in vitro* chromosomal aberration test with Chinese hamster V79 cells," Bayer Healthcare AG, Wuppertal, Germany, 1/16/07. Laboratory Study # T5076831, Report AT03625. Thiencarbazone-methyl (BYH 18636), 94.6% purity, was evaluated at 0 (DMSO control), 100, 200, and 400 µg/ml (with and without S-9 from livers of Aroclor 1254-induced male Sprague-Dawley rats) in a standard chromosomal aberration evaluation with 4 hr exposure and a total of 18 hr to harvest. The same exposure levels were used in 18-hr continuous exposure tests (without S-9 only). For the 4-hr exposure/30 hr harvest studies, only DMSO control and 400 µg/ml thiencarbazone-methyl groups were employed (with and without S-9). Two hrs prior to termination, Colcemid was added to media to arrest cells in c-metaphase. At termination, cells were swollen in hypotonic solution, fixed, and stained with Giemsa solution. At each concentration, coded slides of 100 metaphase spreads from each of two parallel cultures were evaluated. The highest concentration was at the limit of solubility of a.i. in vehicle. Further, media with S-9 activation experienced reduced cell survival at 200 and 400 µg/ml. Thus the dose range was justified. Treatments did not affect chromosomal aberration frequencies nor polyploidy. Mitotic index was unaffected. Positive controls (mitomycin C without S-9, and cyclophosphamide with S-9) were functional. Acceptable, with no adverse effects. Aldous, 9/22/10.

**53100-0066 249820 Thum, M., "BYH 18636: *in vitro* chromosomal aberration test with Chinese hamster V79 cells," Bayer Healthcare AG, Wuppertal, Germany, 9/19/05. Laboratory Study # T1074271, Report AT02499. Thiencarbazone-methyl (BYH 18636), 96.3% purity, was evaluated using treatment levels and methodologies identical to DPR Record No. 249819 (same laboratory and same author). The highest concentration (400 µg/ml) was at the limit of solubility of a.i. in vehicle. Further, media with or without S-9 activation showed modestly reduced cell survival (76-77% of vehicle controls) at 400 µg/ml, thus the selected dose range was justified. Treatments did not affect chromosomal aberration frequencies nor polyploidy. Mitotic index was unaffected. Positive controls (mitomycin C without S-9, and cyclophosphamide with S-9) were functional. Acceptable, with no adverse effects. Aldous, 9/22/10.

DNA DAMAGE

**53100-0066 249823 Herbold, B., "BYH 18636: Micronucleus-test on the male mouse," Bayer Healthcare AG, Wuppertal, Germany, 10/21/04. Laboratory Study # T2074272, Report AT01568. Two NMRI male mice/treatment received thiencarbazone-methyl (BYH 18636), 96.3% purity, Batch 702-73-06-0001, at 0, 125, 250, or 500 mg/kg/day (2 consecutive daily ip injections in 0.5% aq. Cremophor). Positive control was cyclophosphamide (ip, 20 mg/kg). There were 5 male mice per group, with 5 extra "replacement" mice at 500 mg/kg/day. Sacrifice was 24 hrs after the last dose. Investigators isolated erythrocytes from femurs, then evaluated prepared, stained smears for numbers of micronuclei per 2000 polychromatic erythrocytes (PCE's) per mouse, as well as the ratio of normochromatic erythrocytes (NCE's) to PCE's. Systemic toxicity in the 500 mg/kg/day group was demonstrated by 3/10 deaths, plus clinical signs of severe toxicity. There was a statistically elevated micronuclei/PCE value at 500 mg/kg/day thiencarbazone-methyl over concurrent controls. Comparison with contemporary negative controls shows that all treated groups, including 500 mg/kg/day BYH 18636 (thiencarbazone-methyl), were well within the normal range (the high dose group was at the 75th

percentile), whereas values as low as the concurrent control occurred only once out of 44 studies in the most recent 3 years tabulated. Investigators justifiably concluded that this is a valid and negative test. Acceptable, with no adverse effects. Aldous, 9/23/10.

NEUROTOXICITY

**53100-0067 249824 Hoss, H. E., "An acute oral neurotoxicity screening study with Technical Grade BYH 18636 in Wistar rats," Bayer CropScience LP, Stilwell, Kansas, July 5, 2006. Laboratory Study # 05-N12-Z1, Bayer Report No. 201512. Groups of 12 Wistar rats/sex/group were dosed once by gavage with BYH 18636 (thiencarbazone-methyl), 96.1% purity in aq. 0.5% methylcellulose/0.4% Tween 80 at 0, 125, 500, or 2000 mg/kg in a standard acute neurotoxicity study, with FOB and motor observations pre-dose, and at 1 hr, 7 days, and 14 days after dosing. Six/sex/group were perfusion-fixed and stained for neurohistopathology examination, with only control and high dose groups evaluated. Absolute NOEL = 125 mg/kg, based on presence of white material in urine, in bedding material, and in the peri-genital area (each predominantly in males). The white material contained test article. NOEL for transitory behavioral changes = 500 mg/kg, based on reduced motor and locomotor activities in 2000 mg/kg females at 1 hr after dosing, with normal accommodation over assessment intervals. There was no motor/locomotor activity change at 7-day or 14-day intervals. There were no FOB changes observed at any dose level (except white peri-genital area staining in females shortly after dosing, as observed in clinical signs). Rats were grossly normal and microscopically without treatment effects at termination. Study is acceptable, with no adverse effects. Aldous, 9/13/10.

53100-0068 249825 Gilmore, R. G. and H. E. Hoss, "A subchronic neurotoxicity screening study with Technical Grade BYH 18636 in Wistar rats," Bayer CropScience LP, Stilwell, Kansas, 6/26/06. Laboratory Study # 05-N72-AD, Bayer Report No. 201518. Groups of 12 Wistar rats/sex/group were dosed in diet with BYH 18636 (thiencarbazone-methyl), 95.7% purity, at 0, 500, 2000, or 6000 ppm in a standard acute neurotoxicity study, with FOB and motor observations pre-dose and 2, 4, 8, and 13 weeks after dosing. Six/sex/group were perfusion-fixed and stained for neurohistopathology examination, with only control and high dose groups evaluated. Reported estimates of administered dose were 33, 137, and 411 mg/kg/day for respective treated males 42, 171, and 527 mg/kg/day for females. NOEL = 6000 ppm in both sexes (no toxicity observed). **Acceptable, with no adverse effects. Aldous, Nov. 5, 2010.

METABOLISM

Metabolic disposition studies [below] of thiencarbazone-methyl (BYH 18636) in rats indicated about 50% absorption (minimally affected by sex or dose). Technical thiencarbazone-methyl accounted for about 96% of urinary label, and about 88% of fecal label. Initial phase absorption was rapid: $t_{1/2}$ estimates < 1 hr, followed by a much slower phase. About 0.5% of administered dose remained in the carcass after 48 hrs. Tissue concentrations following thiophene-4-¹⁴C treatment were slightly higher in thyroids and plasma than in other tissues. Tissue concentrations following dihydrotriazole-3-¹⁴C treatment highest in liver. Metabolites typically involved breaking of an amide bond between the cyclic constituents.

53100-0069 249830 Justus, K., “[Thiophene-4-¹⁴C] BYH 18636: absorption, distribution, excretion and metabolism in the rat,” Bayer CropScience AG, Monheim am Rhein, Germany, 1/26/06. Laboratory Study # M41819131. Bayer Report No. MEF-05/176. Groups of 4 (usually male) Wistar Hsd/Cpb: WU rats were dosed by gavage with [Thiophene-4-¹⁴C] BYH 18636, as (1) single small (2 mg/kg) doses (male and female), (2) a single large (100 mg/kg) dose, (3) repeated daily dosing at 2 mg/kg/day for 14 days, followed by single administration of 2 mg/kg labeled a.i., or (4) treatment with 2 mg/kg after fitting with bile cannulae to assess biliary excretion. By 48 hrs, over 99% of administered dose had been excreted. Fecal elimination of administered dose (45-60%) slightly exceeded urinary excretion (40-45%). Only 1.5% of administered dose was found in bile, suggesting that fecal label was mostly unabsorbed material. Only about 0.01% of label was obtained in exhaled CO₂. Body burden of administered a.i. after 48 hrs was about 0.5% of administered dose, with concentration highest in liver. Results indicate 40% to 50% absorption, minimally affected by dose or sex. This absorption was rapid: plasma levels peaked by 1 hr after dosing, regardless of sex or dose. Initial first order elimination phase t_{1/2} estimates ranged from 0.1 to 0.6 hrs. Terminal elimination t_{1/2} estimates were 29.3 hrs and 11.5 hrs for low dose males and females, respectively. Multiple dosing terminal elimination t_{1/2} was 7.9 hrs. High dose terminal elimination t_{1/2} was 12.2 hrs. In urine, parent a.i. constituted about 40% of administered dose, with sulfonamide-carboxylic acid as the only significant metabolite, accounting for 1-2% of administered dose. This residue derived via amide bond cleavage to yield a sulfonamide, and loss of a methyl group from the ester group on the thiophene. In feces, about 45% of administered dose was parent compound. About 1% of administered dose was present in feces as BYH 18636-sulfonamide. The only recognizable peak in bile was parent a.i. **Acceptable: this is the major metabolism study, which together with Record No. 249827, fills the metabolism data requirement. Aldous, 10/25/10.

53100-0069 249827 Justus, K., and K. Spiegel, “[Dihydrotriazole-3-¹⁴C] BYH 18636: absorption, distribution, excretion and metabolism in the rat,” Bayer CropScience AG, Monheim am Rhein, Germany, 6/21/06. Laboratory Study # M21819148. Bayer Report No. MEF-06/049. Four male Wistar Hsd/Cpb: WU rats were dosed with were dosed once by gavage with 2.5 mg/kg of [Dihydrotriazole-3-¹⁴C] BYH 18636. Investigators collected urine, feces, and plasma at intervals until 48-hr termination; when blood, organs and tissues were analyzed. Plasma levels peaked at 1 hr, with an initial elimination phase t_{1/2} of 0.3 hrs and a slower terminal elimination t_{1/2} of 35.5 hrs. At 48 hrs, about 54% of administered dose was excreted in urine, vs. 44% in feces. About 0.5% remained with the carcass. Excretion was rapid: urine accounted for 42% of administered dose within 8 hrs, and 43% of administered dose was collected in feces within 24 hrs. Tissue concentrations in thyroids and plasma were slightly higher than in organs such as liver and adrenals at 48 hrs, but no tissue concentration was remarkable. Over 96% of dose recovered in urine was parent thien carbazole-methyl. Otherwise, the urinary metabolite with the greatest concentration was methyl-carbamate, at 0.64% of administered dose. About 88% of fecal radioactivity was parent thien carbazole-methyl. One unknown mobile metabolite accounted for 0.43% of administered dose. There were no other perceptible peaks for fecal extracts. Valid portion of the metabolite series. Aldous, 10/25/10.

SUBCHRONIC STUDIES

**53100-0058 249800 Eigenberg, D. A., "A 90-day toxicity feeding study in the beagle dog with technical grade BYH 18636," Bayer CropScience LP, Stilwell, Kansas, 2/21/07 (amended). Laboratory Study No. 04-S76-WH, Bayer Report No. 201290-1. Groups of four beagles/sex were dosed in diet with BYH 18636 (thiencarbazone-methyl), 95.5% purity, in a subchronic study at 0, 1000, 5000, or 10000 mg/kg/day. Achieved dose levels were 34, 149, and 335 mg/kg/day in treated males, and 32, 159, and 351 mg/kg/day in females. NOEL = 5000 ppm, based on urinary bladder calculus, with associated histopathology such as hemorrhage and epithelial cell hyperplasia: all of these findings in both sexes. Acceptable, with no adverse effects. Aldous, 7/30/10.

**53100-0055 249797 McElligott, A., "BYH 18636: 90-day toxicity study in the rat by dietary administration," Bayer CropScience, Sophia Antipolis, France, Dec. 5, 2003. Laboratory Study # SA 02446. Groups of ten Wistar rats/sex/group were dosed in diet with BYH 18636 (thiencarbazone-methyl), 98 % purity for 90 days at 0, 400, 2000, or 7000 ppm. Corresponding achieved dose levels were 25, 123, and 439 mg/kg/day in treated males, and 31, 154, and 543 mg/kg/day in females. An additional 10/sex were treated for 90 days at 0 or 7000 ppm levels, then maintained off treatment for 30 days for a recovery study. An appropriate neurotoxicity component was included for main study groups. The most sensitive observation was sulfonamide-like crystals in urine of both sexes at 2000 to 7000 ppm, without associated pathology at 2000 ppm. Crystals contained mostly parent test article. A practical NOEL for toxicity would be 2000 ppm, based on findings at 7000 ppm in kidneys (eosinophilic intra-pelvic urolithiasis and collecting duct hyperplasia in both sexes), and in the urinary bladder (eosinophilic urolithiasis in males; and simple, diffuse urothelial hyperplasia in both sexes). Acceptable, with no adverse effects. Aldous, 9/14/10.

53100-0056 249798 Langrand-Lerche, C., "BYH 18636: 90-day toxicity study in the mouse by dietary administration," Bayer CropScience, Sophia Antipolis, France, 2/27/04. Laboratory Study # SA 03086. Groups of ten C57BL/6 mice/sex/group were dosed in diet with BYH 18636 (thiencarbazone-methyl), purity assayed as 98 % to 99.7% (against different standards). Duration was 91-93 days at dose levels of 0, 500, 2000, and 4000 ppm, corresponding to achieved dose levels of 76, 315, and 637 mg/kg/day in treated males, and 103, 409, and 789 mg/kg/day in females. NOEL = 2000 ppm, based on a single male with urinary bladder calculus, diffuse urothelial inflammation, serosal inflammation, submucosal inflammation cell infiltration, and diffuse urothelial hyperplasia. Study is suitable for range-finding for the oncogenicity study which followed, and validates dose selection for that study. No adverse effects. Aldous, Oct. 5, 2010.

SUBCHRONIC STUDIES ON METABOLITES OR ENVIRONMENTAL
DEGRADATION PRODUCTS

53100-0057 249799 Odin-Feurtet, M., "BYH 18636-carboxylic acid: 90-day toxicity study in the rat by dietary administration," Bayer CropScience, Sophia Antipolis, France, 1/18/07. Laboratory Study # SA 06035. Groups of ten Wistar rats/sex/group were dosed in diet with BYH 18636-carboxylic acid [(soil metabolite of thiencarbazone-methyl), 98.7 % purity] for 90 days at 0, 400, 2000, or 15000 ppm. Corresponding achieved dose levels were 25, 127, and 972

mg/kg/day in treated males, and 30, 152, and 1170 mg/kg/day in females. An appropriate neurotoxicity component was included. NOEL = 15000 ppm (highest dose tested). Unlike the parent a.i., this degradate did not lead to urinary crystal formation, nor to pathology of urothelial tissues. There were no remarkable findings. Useful supplementary data, with no adverse effects. No DPR worksheet. Aldous, Sept. 3, 2010.

53100-0054 249796 Rasclé, J. B., "BYH 18636-N-desmethyl (AE 1417257): 28-day toxicity study in the rat by dietary administration," Bayer CropScience, Sophia Antipolis, France, 2/22/07. Laboratory Study # SA 06247. Groups of ten Wistar rats/sex/group were dosed in diet with this plant metabolite of thien carbazole-methyl, 98.9 % purity, for 28 days at 0, 60, 120, 1200, or 12000 ppm. Corresponding achieved dose levels were 5, 10, 106, and 1045 mg/kg/day in treated males, and 5, 11, 116, and 1133 mg/kg/day in females. NOEL = 12000 ppm (highest dose tested). Unlike the parent a.i., this degradate did not lead to urinary crystal formation, nor to pathology of urothelial tissues. There were no remarkable findings. Useful supplementary data, with no adverse effects. No DPR worksheet. Aldous, Sept. 3, 2010.

53100-0070 249838 Rasclé, J. B., "BYH 18636-sulfonamide: 28-day toxicity study in the rat by dietary administration," Bayer CropScience, Sophia Antipolis, France, 1/19/07. Laboratory Study # SA 06084. Groups of ten Wistar rats/sex/group were dosed in diet with this plant metabolite of thien carbazole-methyl, 98.9 % purity, for 28 days at 0, 500, 5000, or 10000 ppm. Corresponding achieved dose levels were 40, 399, and 800 mg/kg/day in treated males, and 47, 460, and 917 mg/kg/day in females. Study included a single FOB and locomotor assessment during week 4. Also, investigators performed ophthalmology, hematology, clinical chemistry, and urinalysis near to study termination. NOEL = 10000 ppm (highest dose tested). Unlike the parent a.i., this metabolite did not lead to urinary crystal formation, nor to pathology of urothelial tissues. There were no remarkable findings. Useful supplementary data, with no adverse effects. No DPR worksheet. Aldous, 9/14/10.

MUTAGENICITY STUDIES ON METABOLITES OR ENVIRONMENTAL DEGRADATION PRODUCTS

53100-0065 249811 Herbold, B., "BYH 18636 N-desmethyl: Salmonella/microsome test: plate incorporation and preincubation method," Bayer Healthcare AG, Wuppertal, Germany, 11/28/06. Laboratory Study # T 9076880, Report AT03497. Test strains were *Salmonella typhimurium*: TA 1535, TA 100, TA 1537, TA 98, and TA 102. Initial test was plate incorporation, with pre-incubation for follow-up, with and without S-9. There were three replicates per step (at 3x intervals). Test article did not induce mutations, with or without S-9. Toxicity, based on diminished revertants at the higher dose level(s), was typically absent or limited to the highest dose level of 5000 µg/plate, in the plate incorporation trial. Useful supplementary data, with no adverse effects. No DPR worksheet. Aldous, 10/27/10.

53100-0065 249812 Wirnitzer, U., "BYH 18636-carboxylic acid: Salmonella/microsome test: plate incorporation and preincubation method," Bayer Healthcare AG, Wuppertal, Germany, Oct. 5, 2006 (as amended). Laboratory Study # T 6073259, Report AT01522A. Test strains were *Salmonella typhimurium*: TA 1535, TA 100, TA 1537, TA 98, and TA 102. Initial test was plate incorporation, with pre-incubation for follow-up, with and without S-9. There were three

replicates per step (at 3x intervals). Test article did not induce mutations, with or without S-9. Toxicity, based on diminished revertants at the higher dose level(s), was typically absent or limited to the highest dose level of 5000 µg/plate. Useful supplementary data, with no adverse effects. No DPR worksheet. Aldous, 9/20/10.

53100-0065 249815 Herbold, B., "BYH 18636 N-desmethyl: V79/HPRT-test *in vitro* for the detection of induced forward mutations," Bayer Healthcare AG, Wuppertal, Germany, 2/26/07. Laboratory Study # T0076881, Report AT03687. Procedure was essentially the same as Record No. 249813, which tested the a.i. Purity of the metabolite in the present study was 98.9%. Material was tested up to and above limits of solubility in vehicle (DMSO). Test article was not cytotoxic at any treatment level, and was negative for mutagenicity. Positive controls were functional. Useful supplementary data. No DPR worksheet. Aldous, 9/21/10.

53100-0066 249818 Herbold, B., "BYH 18636-carboxylic acid: V79/HPRT-test *in vitro* for the detection of induced forward mutations," Bayer Healthcare AG, Wuppertal, Germany, 4/14/05. Laboratory Study # T9073261, Report AT02038. Procedure was essentially the same as Record No. 249813, which tested the a.i. Purity of the metabolite in the present study was 98.5%. Material was tested up to limits of solubility in vehicle (DMSO), 1200 µg/ml. This concentration slightly reduced pH of medium to 6.77. Test article was not cytotoxic at any treatment level, and was negative for mutagenicity. Positive controls were functional. Useful supplementary data. No DPR worksheet. Aldous, 9/21/10.

53100-0066 249821 Nern, M., "BYH 18636 N-desmethyl: *in vitro* chromosomal aberration test with Chinese hamster V79 cells," Bayer Healthcare AG, Wuppertal, Germany, 2/16/07. Laboratory Study # T1076882, Report AT03678. Procedure was essentially the same as Record No. 249819, which tested the a.i. Purity of the metabolite in the present study was 98.9%. The highest concentration used (1300 µg/ml) was at the limit of solubility of test article in vehicle. Aside from a modest reduction in mitotic index at 1300 µg/ml with S-9 activation following a 4-hr exposure and 8 hr harvest time, there were no treatment effects noted. Particularly, treatments did not affect chromosomal aberration frequencies nor polyploidy. Positive controls (mitomycin C without S-9, and cyclophosphamide with S-9) were functional. Valid supplementary data, with no adverse effects. No DPR worksheet. Aldous, 9/22/10.

53100-0066 249822 Herbold, B., "BYH 18636-carboxylic acid: *in vitro* chromosomal aberration test with Chinese hamster V79 cells," Bayer Healthcare AG, Wuppertal, Germany, 3/29/05. Laboratory Study # T8073260, Report AT01980. Procedure was essentially the same as Record No. 249819, which tested the a.i. Purity of the test article in the present study was 98.5%. Dose levels were 300, 600, 1200 µg/ml. The highest concentration was just above the limit of solubility of test article in vehicle. At that concentration, pH was reduced to 6.7. Treatments did not systematically affect chromosomal aberration frequencies, polyploidy, survival or mitotic indices, although the mid-dose group was in some cases statistically significantly different from concurrent controls. Differences in this group were not large, and these findings appear to be incidental. In particular, chromosomal aberrations (excluding gaps) for 4 hrs treatment/18 hr harvest with activation averaged 3, 6, 8 [significant, $p < 0.05$], and 4 for test article concentrations of 0, 300, 600, and 1200 µg/ml. This was the only significant value for test article for chromosomal aberrations. There was no increase (with or without S-9) in the 4 hrs treatment/30 hr harvest test. The noted significant value was within historical range.

Positive controls (mitomycin C without S-9, and cyclophosphamide with S-9) were functional. Valid supplementary data, with no adverse effects. No DPR worksheet. Aldous, 9/22/10.

53100-0071 249839 Herbold, B., "BYH 18636 Sulfonamide: Salmonella/microsome test: plate incorporation and preincubation method," Bayer Healthcare AG, Wuppertal, Germany, 12/15/06. Laboratory Study # T 5076444, Report AT03605. Test strains were *Salmonella typhimurium*: TA 1535, TA 100, TA 1537, TA 98, and TA 102. This sulfonamide was Batch CHZC007326, purity 99.0%. Initial test was plate incorporation, with pre-incubation for follow-up, with and without S-9. There were three replicates per step (at 3x intervals). Test article did not induce mutations, with or without S-9. Toxicity, based on diminished revertants at the higher dose level(s), was absent up to at least 5000 µg/plate. Useful supplementary data, with no adverse effects. No DPR worksheet. Aldous, 10/19/10.

STUDY WAIVER REQUESTS

53100-0070 249837 Zhou, J., "Waiver request for 21-day dermal study on BYH 18636," Bayer CropScience, Research Triangle Park, NC, March 12, 2005. Registrant requests waiver on the 21-day dermal study based on demonstrated low toxicity (citing acute oral and dermal toxicity studies), limited dermal penetration, and high LD₅₀'s in subchronic studies. Data suggest that performing this additional study would not justify its use of animals. Aldous, 9/14/10.

STUDY TYPES NOT ASSIGNED TO MEDICAL TOXICOLOGY BRANCH FOR REVIEW

53100-0069 249831 Capt, A., "[¹⁴C]-BYH 18636 in SC450 formulation: comparative *in vitro* dermal absorption study using human and rat skin," Bayer CropScience, Sophia Antipolis, France, Sept. 5, 2006. Study type is reviewed by Worker Health and Safety Branch of DPR.