

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY  
DEPARTMENT OF PESTICIDE REGULATION  
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA  
SPIROTETRAMAT (BYI 08330)

Chemical Code # 5955, Document Processing Number (DPN) # 53020  
SB 950 # N/A  
12/7/07

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, possible 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
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, possible adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Study not required at this time

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Toxicology one-liners are attached.

All record numbers for the above study types through 228895 (vol. no. 53020-0201) were examined.

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: T071207

Revised by Moore, 12/07/07

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

### COMBINED, RAT

Please find separate entries for chronic and oncogenicity rat, below.

#### CHRONIC TOXICITY, RAT

**\*\*53020-0147 228841** Wahle, B. S., "Technical grade BYI 08330 (Common name Spirotetramat): a chronic toxicity testing study in the rat," Bayer CropScience LP, Stilwell, KS, 11/15/05. Bayer Report # 201285. Twenty-five Wistar Hanover rats/sex/group were dosed in diet with Spirotetramat (BYI 08330), Lot/Batch # 08045/0014, purity 97.5%, at 0, 250, 3500, or 7500♂/12000♀ppm, for 1 year in a chronic study with an FOB component. Achieved dose levels were 13.2, 189, and 414 mg/kg/day in treated males, and 18.0, 255, and 890 mg/kg/day in females. NOEL = 250 ppm (male) and 3500 ppm (female), both based primarily on alveolar macrophage accumulation in the lungs. Males at 7500 ppm had occasional cases of abnormal spermatozoa in testes and exfoliated germ cells and debris in epididymides, plausibly treatment-related. At 12000 ppm, females also displayed an increase in yellow and brown staining, especially in the urogenital area and on the tail. Study is acceptable, with no adverse effects. Aldous, 11/16/07.

#### CHRONIC TOXICITY, DOG

**\*\*53020-0148 228842** Eigenberg, D. A., "A chronic toxicity feeding study in the beagle dog with Technical Grade BYI 08830," Bayer CropScience LP, Stilwell, KS, July 6, 2006, Bayer Report #201486. Four beagles/sex/group were dosed in diet for 1 year with 0, 200, 600, or 1800 ppm of Spirotetramat (BYI 08330), Lot/Batch # 08045/0014, purity 97.8%. Estimated achieved dose levels were 6, 20, and 55 mg/kg/day in treated males, and 5, 19, and 48 mg/kg/day in treated females. There is no NOEL in this study for either sex: there was a consistent dose-related decrement in T4 concentrations in males and females throughout the study. In addition, T3 was modestly but consistently reduced in 1800 ppm males during the treatment period. A NOAEL of 600 ppm is supportable, due to responses in 1800 ppm males. The latter group had two dogs with subtle thyroid changes (reduced size of peripheral follicles). A single male with the most extensive of the latter findings also had exceedingly low circulating T4 levels, and had frequent clinical signs which may have been related to thyroid deficiency, such as "ataxia," "decreased activity," "unsteady," and "lying on side." These findings define the LOAEL. Acceptable, with the above thyroid-associated changes as "possible adverse effects." Aldous, 11/27/07.

#### ONCOGENICITY, RAT

**\*\*53020-0149 228843** Wahle, B. S., "Technical grade BYI 08330 (Common name Spirotetramat): an oncogenicity testing study in the rat," Bayer CropScience LP, Stilwell, KS, 5/31/06. Bayer Report No. 201358. Groups of 55 Wistar Hanover - CrI:WI[Glx/BRL/Han]IGS BR rats/sex/group were dosed in diet for 2 years with Spirotetramat (BYI 08330), purity 97.5% in a standard oncogenicity study at 0, 250, 3500, or 7500♂/12000♀ppm, equivalent to mean exposures of 12.5, 169, or 373 mg/kg/day in males, or 16.8, 229, or 823 mg/kg/day in females. NOEL = 250 ppm. Findings at 3500 ppm included "dilatation of renal tubules in a distinct zone of the outer medullae" (both sexes), and possibly also lung lesions of a continuum ranging from increased accumulations of alveolar macrophages to interstitial pneumonia (marginally significant in 3500 ppm females). Respective high dose effects included body weight decrements (decrements of 10% in males and 14% in females at termination); "scaly" skin and staining in females (stains yellow or brown, typically perigenital, perianal, or on the tail); a pronounced increase in immature or exfoliated germ cells in epididymides and an elevation of a minor grade of testicular change characterized as "spermatid degeneration/depletion/asynchrony." Study is acceptable, with no adverse effects. Aldous, 11/26/07.

### ONCOGENICITY, MOUSE

**\*\*53020-0150 228844** Wahle, B. S., "Technical grade BYI 08330 (Common name Spirotetramat): an oncogenicity testing study in the mouse," Bayer CropScience LP, Stilwell, KS, 3/19/06. Bayer Report # 201359-1. Fifty-five CD-1 ([ICR]/BR) mice/sex/group were dosed in diet for 18 months with Spirotetramat, Lot/Batch # 08045/0014, purity 97.5%. Dose levels were 0, 70, 1700, or 7000 ppm (reduced at week 12 to 6000 ppm), equivalent to an average of 11, 263, or 1022 mg/kg/day in males and 14, 331, and 1319 mg/kg/day in females. NOEL = 6000/7000 ppm in females (1319 mg/kg/day: the highest dose tested) and 1700 ppm in males (263 mg/kg/day), based on the presence of two rare subcutaneous benign lipomatous tumors in high dose males (none in other groups of either sex), a finding possibly related to treatment. Study is **acceptable**, with a "**possible adverse effect**," considering the low likelihood of 2 cases of lipomatous tumors occurring by chance. Considering that the tumors were benign and superficially located, that there were no associated circumstances to corroborate a treatment effect, and that the apparent NOEL was quite high, the apparent concern for this finding is comparatively minor. Aldous, 11/27/07.

### REPRODUCTION, RAT

**\*\*53020-0146 228840** Young, A. D., "Technical grade BYI 08330 (Common name Spirotetramat): Reproduction and fertility effects study - rat" (Revised Report), Bayer CropScience LP, Stilwell, KS, 7/13/06. Bayer Report # 201426-1. Groups of 30 Wistar Hanover - Crl:WI[Glx/BRL/Han]IGS BR rats/sex/group were treated continuously in a standard reproduction study (1 littering period per generation) at dietary levels of 0, 250, 1000, or 6000 ppm spirotetramat, purity 97.8%, (corresponding to pre-mating period exposures of 17.2, 71, and 419 mg/kg/day, respectively, in F0 males, 20.0, 82, and 485 mg/kg/day in F0 females, 19.3, 80, and 487 mg/kg/day in F1 males, and 21.7, 90, and 540 mg/kg/day in F1 females). Parental systemic toxicity NOEL = 250 ppm (decreased kidney weights in F1 adult males). Parental reproductive effects NOEL = 1000 ppm in males (abnormal spermatozoa in one 6000 ppm male), and 6000 ppm in females (no reproductive effects observed). Offspring viability and growth NOEL = 1000 ppm (reduced pup body weight gain during lactation, associated with significantly reduced maternal food intake). **Acceptable, with no adverse effects.** Note that investigators considered the decreased kidney weights, cited above as the basis of a parental systemic toxicity NOEL, to be incidental findings. Investigators may submit relevant historical kidney weight historical control data for re-visiting this conclusion. Parental systemic toxicity indicators at 6000 ppm included reduced body weights in F1 males and females, and a high incidence of kidney tubular dilatation (chiefly at the outer portion of the medulla) in F1 males and females. Slightly reduced splenic weights in males and females was an equivocal effect (without associated histopathology). Aldous, Dec. 5, 2007.

53020-0170 228864 Young, A. D., "Technical grade BYI: A dose range-finding reproductive toxicity study in the Wistar rat," Bayer CropScience LP, Stilwell, KS, 7/12/06. Bayer Report # 201300-1. Groups of 10 Wistar Hanover - Crl:WI[Glx/BRL/Han]IGS BR rats/sex/group were treated continuously throughout the in-life portion of this pilot study (1 generation, 1 littering period) at dietary levels of 0, 200, 500, 6000, or 10000 ppm. Parental rats were terminated shortly after the last litters were produced (males) or following weaning of litters (females). Some pups were maintained long enough to assess developmental landmarks of vaginal opening or preputial separation. Young adult F1 males were also assessed for sperm analysis. The 10000 ppm group mated, but did not produce implantations. The 6000 ppm group had normal gestation outcomes and normal lactation indices, however these pups had significantly reduced body weights compared to controls. F1 males weighed significantly less than controls at termination (8-9 weeks). There was an elevation in incidence of abnormal epididymal sperm at 6000 ppm in F1 males [about 10% (20.2/200) of sperm with amorphous heads in 6000 ppm F1 males, compared to  $\leq$  1.4% in other groups (1.3-2.8/200)]. About 48% (95.5/200) of sperm in 10,000 ppm F0 males had amorphous heads, compared to  $\leq$  0.4% (0.5 to 0.8/200) in other

groups. This pilot study identifies the probable reproductive toxicity for the definitive study, and justifies the dose selection for that study. Aldous, 11/27/07 (no DPR worksheet).

53020-0168 228862 Kennel, P., "BYI 08330: Evaluation of the potential reproductive toxicity in the male rat following daily oral administration by gavage," Bayer CropScience, Sophia Antipolis, France, 5/23/05. Laboratory Study #: SA 04181. Male Wistar Hanover - Crl:WI[Glx/BRL/Han]IGS BR rats, 8/dosing duration/group were dosed daily by gavage in 0.5% methylcellulose with 0 or 1000 mg/kg/day Spirotetramat (BYI 08330) for 3, 10, 21, or 41 days. At sacrifice, each left testis and left epididymis was examined microscopically. Sperm count and morphology analyses were performed in the right epididymides. Food consumption was reduced sharply early in the study, with a return to normal as the study progressed. Body weight was significantly reduced (by 33 g at day 15, and by 57 g at day 41). One treated rat died, and 8/32 treated rats had urine-stained fur. Percent abnormal spermatozoa, ranging from 2.5 to 4.1% in controls, was modestly but significantly elevated to 6.4% by day 21, and was 72.0% at day 41. Epididymal sperm count was not consistently affected through day 21, but was reduced by 75% (absolute) or 68% (per g caudal epididymis) at day 41. Weights of testes and epididymides were significantly reduced at day 41, but were unaffected at earlier times. Beginning at day 21, epididymides showed increased intraluminal aberrant cell types, and testes had degeneration of round spermatids and elongating spermatids, with some multinucleated giant spermatids. All of these findings were observed at day 41, typically at higher incidence and/or severity. In addition, at day 41, all epididymides displayed oligospermia, and testes showed losses of elongating spermatids and Sertoli cell vacuolation. Investigators determined that primary toxicity had occurred at round spermatid or late spermatocyte stages, based on the temporal patterns and cell stages affected. Useful supplementary data. C. Aldous, Dec. 4, 2007.

#### TERATOLOGY, RAT

\*\* 0143, 228837; "BYI 08330: Developmental Toxicity Study in Rats After Oral Administration" (Klaus, A.-M., Bayer HealthCare AG, PH-PD Toxicology International, Wuppertal, Germany, Report of Study T9062786, 08/23/04). 870.37. BYI 08330 (Batch no. NLL 6425-14-a, purity = 99.0%) was suspended in 0.5% aqueous carboxymethylcellulose and administered as a single daily dose by gavage to 25 pregnant Wistar (HsdCpb:WU) rats per dose at dose levels 0 (0.5% aqueous carboxymethylcellulose), 20, 140, or 1000 mg/kg/day from gestation day 6 to gestation day 19. No maternal deaths were observed. Treatment-related decreases in dam body weight gain and food consumption were observed at 1000 mg/kg/day. No treatment-related clinical signs were observed in the dams during gestation. Macroscopic examination of the dams revealed no treatment-related abnormalities. Analyses of mean number of fetuses per animal, and the mean number of resorptions per animal revealed no treatment-related effects. A decrease in mean fetal weight at 1000 mg/kg/day was observed. No treatment-related fetal visceral malformations were observed. Treatment-related incidences of fetal skeletal malformations on a litter basis at 1000 mg/kg/day included incompletely ossified 3<sup>rd</sup> and 4<sup>th</sup> proximal phalanx digits, incompletely ossified 3<sup>rd</sup> distal phalanx toes, incompletely ossified 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, and 6<sup>th</sup> sternbrae, wavy ribs (3<sup>rd</sup> through 13<sup>th</sup>), incompletely ossified cervical vertebrae (3<sup>rd</sup> through 6<sup>th</sup>), incompletely ossified 4<sup>th</sup> sacral arches (left and right), incompletely ossified nasal bone (bilateral), incompletely ossified temporal bone, and incompletely ossified zygomatic bone. No dose-related skeletal malformations on a litter basis were observed at the low and mid-doses. **No adverse effects. Maternal NOEL= 140 mg/kg/day** (based on decreased body weight gain and food consumption) **Developmental NOEL = 140 mg/kg/day** (based on decreased fetal weight and incompletely ossified fetal skeletal structures). **Acceptable.** (Corlett and Leung, 10/16/07)

\*\*53020-0145 228839 Klaus, A. -M., "BYI 08830 [Synonym: FHN 08330]: Supplementary developmental toxicity study in rats after oral administration," Bayer HealthCare AG, Wuppertal,

Germany, Oct. 7, 2004. Laboratory Study #: T 7063008, Report No. AT01512. Groups of 25 SPF-bred Wistar derived [Hsd Cpb:WU] mated females were dosed by gavage with 0, 10, 35, or 140 mg/kg/day Spirotetramat (BYI 08830), purity 99.1%, Batch NLL 6425-14-a, in 0.5% aq. CMC, 10 ml/kg b.w., on gestation days 6 to 19 in a supplementary guideline rat developmental toxicity study. This study sought to clarify findings of the original rat developmental toxicity study: 53020-0143 228837 Klaus, A. -M., BYI 08330 - developmental toxicity study in rats after oral administration," Bayer HealthCare AG, Wuppertal, Germany, 8/23/04, Laboratory Study # T 9062786, Report No. AT01413. These two studies were examined collectively to assess NOEL's. Maternal toxicity NOEL = 140 mg/kg/day (no maternal toxicity observed in this study, and no definitive maternal toxicity at this dose in the original developmental toxicity study). The present study did not identify developmental toxicity. Developmental toxicity NOEL considering these studies together = 140 mg/kg/day. The present study is acceptable, with no adverse effects. Aldous, 11/30/07.

53020-0159 228853 Klaus, A. -M., "BYI 08830: pilot study on developmental toxicity in rats after oral administration," Bayer HealthCare AG, Wuppertal, Germany, May 8, 2001. Laboratory Study #: T 3068559, Report No. MO-01-009538. Groups of at least 7 mated Wistar females were dosed orally with 0, 50, 200, 800, and 1000 mg/kg/day of Spirotetramat by gavage in 0.5% aq. CMC, 10 ml/kg b.w. from gestation days 6-19. Dams administered 1000 mg/kg/day displayed transient gasping, increased or decreased water intake, piloerection, increased urination, and light-colored feces. Body weight and food consumption reductions were evident throughout the treatment period at 1000 mg/kg/day. There was a slight apparent body weight decrement at 800 mg/kg/day. Apparently 800 to 1000 mg/kg/day led to reduced placental weights and possibly reduced fetal weight, delayed ossification, and wavy ribs. This record did not provide sufficient information for review, and is superceded by two subsequent developmental toxicity studies (the original study summarized immediately, below, and the record reviewed in this review). No DPR worksheet for this pilot study. Aldous, 11/30/07.

#### TERATOLOGY, RABBIT

\*\*53020-0144 228838 Klaus, A. -M., "BYI 08830: Developmental toxicity study in rabbits after oral administration," Bayer HealthCare, Wuppertal, Germany, 2/17/04. Report # AT01003. Laboratory Study # T 3063167. Groups of 22 mated Himalayan CHBB:HM rabbits were dosed with 0, 10, 40, and 160 mg/kg/day of Spirotetramat (BYI 08830), purity 98.9%, Batch 08045/0004 by gavage in suspensions of 0.5% CMC in demineralized water, 5 ml/kg b.w. Additional does were placed in the two higher dose groups to replace non-pregnant does or non-survivors. Maternal toxicity NOEL = 10 mg/kg/day (1 and 2 abortions respectively in 40 mg/kg/day and 160 mg/kg/day does). Six 160 mg/kg/day does died or were killed *in extremis*: the most common associated signs were cold ears, soft feces, reduced feces, and the related cluster of decreased water consumption, decreased urination, and darkened urine color. Developmental toxicity NOEL = 10 mg/kg/day ( the variation: "distinct liver lobulation" was observed in 2 litters including 8 fetuses at 160 mg/kg/day, and in 1 litter including 2 fetuses at 40 mg/kg/day). Both maternal and fetal NOEL's are conservative assessments based apparent dose-responses of events which are not uncommon. Acceptable, with no adverse effects. Aldous, 11/30/07.

53020-0169 228863 Holzum, B., "BYI 08830: Pilot developmental toxicity study in rabbits after oral administration," Bayer HealthCare AG, Wuppertal, Germany, 11/14/01. Laboratory Study #: T 3062735; Report No. MO-01-020840. Three Himalayan rabbits/group were dosed by gavage in aq. 0.5% CMC at 0, 5, 25, 100, 160, 250, or 500 mg/kg/day on gestation days 6-28. All 500 mg/kg/day does died or were killed *in extremis* by gestation day 18. At 250 mg/kg/day, one doe was killed *in extremis*, one aborted, and one had total resorptions, hence there were no litters at that dose level. Findings at 160 mg/kg/day included does with cold ears, decreased feed intake, and increased body weight losses, but all survived. There were no definitive effects

on fetuses at 160 mg/kg/day or below. This dose was thus chosen for the primary developmental toxicity study. Useful supplementary data, no DPR worksheet. Aldous, 10/5/07.

### GENE MUTATION

\*\*53020-0152 228846 Herbold, B., "BYI 08330: Salmonella/microsome test, plate incorporation and preincubation method," Bayer HealthCare, Wuppertal, 10/24/02. Bayer Study # T 5071214, Report # AT00056. Salmonella typhimurium strains TA 98, TA 100, TA 102, TA 1535, and TA 1537 were exposed to Spirotetramat (BYI 08330), Batch No. NLL6425-9, purity 93.5%, at 16, 50, 158, 500, 1581, and 5000 µg/plate. Triplicate plates were assessed by both plate incorporation and preincubation methods, with and without S-9. There were functional positive controls in all cases. Cytotoxicity was evident by reduced cell titers and by reduced background lawn appearance: such toxicity was variable, but on average was manifest at 1581 µg/plate and above. Study is acceptable, with no adverse effects. Aldous, 4/25/07.

\*\*53020-0151 228845 Herbold, B., "BYI 08330: Salmonella/microsome test, plate incorporation and preincubation method," Bayer HealthCare, Wuppertal, 5/24/06. Bayer Study No. T 6076454, Report No. AT03070 Salmonella typhimurium strains TA 98, TA 100, TA 102, TA 1535, and TA 1537 were exposed to Spirotetramat (BYI 08330), Batch No. SAV550-085/2, purity 95.2%, at 16, 50, 158, 500, 1581, and 5000 µg/plate. Triplicate plates were assessed by both plate incorporation and preincubation methods, with and without S-9. There were functional positive controls in all cases. Cytotoxicity was evident by reduced cell titers and by reduced background lawn appearance: such toxicity was variable, but on average was manifest at 1581 µg/plate and above. Study is acceptable, with no adverse effects. This study is comparable to Record No. 228846, performed by the same investigator 4 years earlier, in all significant aspects. These two studies used different batches of test article. Aldous, 4/26/07.

\*\*53020-0153 228847 Herbold, B., "BYI 08330: V79/HPRT-test in vitro for the detection of induced forward mutations," Bayer HealthCare, Wuppertal, amended report date: 1/24/03. Bayer Study No. T 7071478, Report No. AT00137A. Spirotetramat (BYI 08330), purity 93.5%, Batch No. NLL6425-9, was tested in V79 cell cultures for forward mutations (based on resistance to 6-thioguanine lethality) with and without S-9, each in three independent trials, at closely-spaced concentrations up to the limits of cell survival and colony growth, with each dose level prepared in duplicate in each trial. Positive controls were ethylmethanesulfonate (EMS) without S-9 and dimethylbenzanthracene (DMBA) with S-9: both were effective. There were no replicable increases in mutant frequency. Study is acceptable, with no adverse effects. Aldous, 4/30/07.

### Gene Mutation Studies with Metabolites or Other Analogs of Spirotetramat:

53020-0195 228889 Wurnitzer, U., "BYI 08330-desmethyl-ketohydroxy (Project: BYI 08330) Salmonella/microsome test, plate incorporation and preincubation method," Bayer HealthCare, Wuppertal, 5/9/06. Bayer Study No. T 2076126, Report No. AT03027. Study design was comparable to spirotetramat studies such as Record Nos. 228845 and 228846. There were functional positive controls in all cases. Slight cytotoxicity was evident in some strains by reduced cell titers and/or by reduced background lawn appearance, but test article was less toxic than spirotetramat. Valid supplementary study with no mutagenicity indicated. Aldous, 4/26/07.

53020-0201 228895 Herbold, B., "BYI 08330-mono-hydroxy (Project: BYI 08330) Salmonella/microsome test, plate incorporation and preincubation method," Bayer HealthCare, Wuppertal, 12/13/05. Bayer Study No. T 8075772, Report No. AT02716. Study design was comparable to spirotetramat studies such as Record Nos. 228845 and 228846. There were functional positive controls in all cases. No cytotoxicity was evident: cell titers were unaffected

and background lawn appearance was normal in all cases. Valid supplementary study with no mutagenicity indicated. Aldous, 4/26/07.

53020-0192 228886 Herbold, B., "BYI 08330-CIS-ketohydroxy (Project: BYI 08330) Salmonella/microsome test, plate incorporation and preincubation method," Bayer HealthCare, Wuppertal, 12/15/05. Bayer Study No. T 3075731, Report No. AT02735. Study design was comparable to spirotetramat studies such as Record Nos. 228845 and 228846. There were functional positive controls in all cases. Some cytotoxicity was evident in some strains by reduced cell titers and/or by reduced background lawn appearance. This toxicity was evident in all 5 strains in the preincubation method only, and was limited to the 5000 µg/plate groups. Valid supplementary study with no mutagenicity indicated. Aldous, 4/26/07.

53020-0197 228891 Herbold, B., "BYI 08330-di-hydroxy (Project: BYI 08330) Salmonella/microsome test, plate incorporation and preincubation method," Bayer HealthCare, Wuppertal, 5/24/06. Bayer Study No. T 7076437, Report No. AT03069. Study design was comparable to spirotetramat studies such as Record Nos. 228845 and 228846. There were functional positive controls in all cases. No cytotoxicity was evident: cell titers were unaffected and background lawn appearance was normal in all cases. Valid supplementary study with no mutagenicity indicated. Aldous, 4/26/07.

### CHROMOSOME EFFECTS

**\*\*53020-0154 228848** Herbold, B., "*In vitro* chromosomal aberration test with Chinese Hamster V79 cells," Bayer HealthCare, Wuppertal, 10/24/02. Laboratory Study # T 6071477. Spirotetramat (96.5%) was evaluated at 10, 30, and 50 µg/ml (without S-9) or 20, 40, and 80 µg/ml (with S-9) in a standard chromosomal aberration evaluation with 4 hr exposure and a total of 18 hr to harvest (these dose levels had been properly chosen considering survival limitations). There were 200 spreads examined per dose level. Positive controls were viable. At the highest dose levels with and without S-9, but not at lower dose levels, there were significant increases in metaphases with chromosomal aberrations. In a second trial (4 hr treatment, total of 30 hr until harvest, respective highest doses with and without S-9), there was no treatment effect without S-9, but there was a significant increase with the highest group with S-9 (80 µg/ml spirotetramat). Investigators then determined that appropriate dose regimens for 18 hr continuous treatment (18 total hrs to harvest) were 12, 24, and 48 µg/ml without S-9. Under these circumstances, there was a significant increase of chromosomal aberrations at 48 µg/ml only. Investigators justifiably considered there to be a weak positive chromosomal aberration effect. A supplementary study was later undertaken (see Record No. 228849). Acceptable, with a "possible adverse effect." Aldous, Dec. 5, 2007.

53020-0155 228849, Herbold, B., "Cytogenetic screening with Chinese Hamster V79 cells," Bayer HealthCare, Wuppertal, 1/13/03. Laboratory Study # T 5072033. This is a supplement to the primary study of this type (Record No. 228848). In the present study, only one dose level with and one without S-9 were read, these being the highest levels supportable based on survival and mitotic indices. Selected levels examined were 70 µg/ml without S-9 and 120 µg/ml with S-9. There was no chromosomal aberration response in either case. In this supplementary study there were no positive controls. As was the case in the primary study, there was no effect on polyploid metaphases. Useful supplementary data. Aldous, 4/23/07.

**\*\*53020-0158 228852** Herbold, B., "Chromosomal aberration assay in bone marrow cells of the mouse with BY 08330," RCC Cytotest Cell Research, Rossdorf, Germany, 3/24/03. Bayer Study# T 4072032. Six male NMRI mice/group were dosed ip with 0, 125, 250, or 500 mg/kg Spirotetramat (BYI 08330), purity 92.7%, in 10 ml/kg of 0.5% Cremophor suspension 24 prior to sacrifice for analysis of femoral bone marrow chromosomal aberrations. Mice were dosed 2.5 hr before sacrifice with colcemid to arrest cells in metaphase. A functional positive control

group was dosed with cyclophosphamide 24 hr before sacrifice. An additional spirotetramat group was dosed with 500 mg/kg 48 hr prior to sacrifice. One hundred cells were scored per mouse, and 5 preparations were analyzed per group. There was no effect on chromosomal aberrations. Study is acceptable, with no adverse effects. Aldous, 4/23/07.

\*\*53020-0156 228850 Herbold, B., "BYI 08330: Micronucleus-test on the male mouse," Bayer HealthCare, Wuppertal, 10/24/02. Bayer Study No. T 8071479. Five male mice/group were treated with Spirotetramat (BYI 08330), purity assayed at 96.5% and 93.5% at times bracketing the dosing period. Dose levels were 0, 125, 250, or 500 mg/kg/day, each level administered ip (in 10 ml/kg of 0.5% Cremophor suspension) twice at 24 hr intervals, with sacrifice 24 hr after the second treatment. An additional set of five 500 mg/kg/day mice was treated to be used in the case of excess mortality at that dose. A set of 5 positive controls were dosed once with 20 mg/kg cyclophosphamide 24 hr before sacrifice. At least one femur per mouse was used to obtain marrow cells, and 2000 PCE's were evaluated per mouse from the stained smears. The study was negative and acceptable. Aldous, 4/24/07.

### DNA DAMAGE

\*\*53020-0157 228851 Brendler-Schwaab, S., "BYI 08330: Unscheduled DNA synthesis test with rat liver cells *in vivo*," Bayer HealthCare, Wuppertal, July 10, 2003. Bayer Study No. T3072031. Groups of 4 Crl:(WI)BR male rats were dosed with Spirotetramat (BYI 08330), 92.7% purity, as a single gavage dose of 0, 1000, or 2000 mg/kg in 10 ml/kg of 0.5% Cremophor suspension, either 4 hr or 16 hr prior to sacrifice. Positive controls, N,N'-Dimethylhydrazine for the 4 hr sacrifice, and 2-Acetylaminofluorene for the 16 hr sacrifice, were functional. Both spirotetramat treatment groups elicited clinical signs such as roughened fur and rapid breathing, but doses were not lethal. Rats were anesthetized, livers were perfused with a buffer containing collagenase, hepatocytes were collected, allocated to wells containing about  $3.75 \times 10^5$  cells, and incubated for 4 hr with  $^3\text{H}$ -thymidine. After replacement with fresh medium, citrate salts were added to swell the nuclei, and cells were fixed and subjected to autoradiography and staining of the cells. Investigators evaluated net nuclear grain (NNG) counts for each of 150 cells/rat by subtracting mean counts from 3 cytoplasmic areas of equal area to the nucleus. Spirotetramat was negative at both treatment levels and both pre-treatment times. Tests for experimental validity were met. The study is acceptable, with no adverse effects. Aldous, 4/25/07.

### NEUROTOXICITY

#### Rat Acute Neurotoxicity Study

0160, 228854; "An Acute Oral Neurotoxicity Screening Study with Technical Grade BYI 08330 in Wistar Rats" (Gilmore, R.G. and Fickbohm, B.L., Bayer CropScience LP, Toxicology, Stilwell, KS, Report No 201283, 04/13/05). 870.62. Technical Grade BYI 08330 (Batch No.: Mixed-Batch 08045/0014, purity = 97.8-98.5%), suspended in 0.5% methylcellulose/0.4% Tween 80 in deionized water, was administered as a single gavage dose to 12 Wistar rats per sex per dose at nominal dose levels of 0 (vehicle only), 200, 500, and 2000 mg/kg (initial study), with a follow-up study consisting of 12 Wistar rats per sex per dose at nominal dose levels of 0 (vehicle only), 50, 100, and 500 mg/kg. No treatment-related mortalities occurred. Treatment-related urine staining was observed (cage-side observations) at all dose levels (200, 500, and 2000 mg/kg) in the initial study but only in females at 500 mg/kg in the follow-up study. No effects on body weight were observed. FOB assessments revealed no treatment-related effects on days 0, 7, and 14. Treatment-related decreases in motor activity (in males and females at 2000 mg/kg) and locomotor activity (in males at 500 and 2000 mg/kg and in females at 2000 mg/kg) were observed in the initial study on the day of dosing but not on days 7 and 14; no treatment-related effects on motor or locomotor activity were observed in the follow-up study animals. Macroscopic and microscopic examinations revealed no treatment-related abnormalities. NOEL (M/F) = 100 mg/kg (based on urine staining and decreased motor and

locomotor activity). **Unacceptable but possibly upgradable** with the submission of more recent positive control data specifically more recent FOB with carbaryl, FOB and neuropathology with acrylamide, and neuropathology with trimethyltin data generated within a few years of the time interval of the study in review. (Corlett and Leung, 08/28/07)

## **SUBCHRONIC AND SUBACUTE STUDIES**

### **Mouse Subacute Dietary Toxicity Study**

0137; 228831; "BYI 08330 Subacute Study with Mice (Keto-Enol Design)" (Schladt, L., Bayer HealthCare AG, PH-GDD-Toxicology, Wuppertal, Germany, Study No. T 2070951 (Report Number MO-02-002425, 09/13/01). BYI 08330 (no lot number provided, no information on purity provided) was administered in the feed to 5 CD-1 male mice per dose at levels of 0, 500, or 5000 ppm (0, 136.5, and 1415.2 mg/kg/day) for 4 weeks. No mortalities occurred. No clinical signs were observed. No effect on body weight was observed. Decreased food intake was observed at 500 and 5000 ppm. No treatment related effects on serum alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, cholesterol, and triglyceride concentrations were observed. No treatment-related effects on the weights of selected internal organs (adrenals, liver, testes, and epididymides) were observed. Histopathological examination of the liver, adrenal glands, and testes revealed no dose-related changes. NOEL (M) not determined. **Supplemental study** ((1) only male animals were used, (2) only 5 animals per dose level were used, (3) only 2 dose levels were used, and (4) no hematology or ophthalmology were conducted on the test animals). (Corlett, 09/20/07)

### **Mouse Subchronic Dietary Toxicity Study**

53020-0140 228834 Wahle, B. S., "Technical grade BYI 08330: a subchronic toxicity testing study in the mouse," Bayer CropScience LP, Stilwell, KS, 7/14/05. Bayer Report # 201284. Fifteen CD-1 ([ICR]/BR) mice/sex/group were dosed in diet for 3 months with Spirotetramat, Lot/Batch # NLL 6425-9, purity 96.5%. Dose levels were 0, 70, 350, 1700, or 7000 ppm, equivalent to an average of 13, 60, 300, or 1305 mg/kg/day in males and 16, 72, 389, and 1515 mg/kg/day in females. Study included terminal hematology and a limited clinical chemistry evaluation, in addition to assessing body weight and food consumption effects, none of which indicated toxicity. Gross necropsy and organ weight data were negative. Only controls and high dose mice were evaluated for histopathology. There was a statistically significant increase in chronic inflammation of the kidney in high dose females compared to controls (5 controls vs 13 high dose females: no change in mean severity grade). There was an apparent NOEL of 7000 ppm for males (1305 mg/kg/day) and 1700 ppm for females (389 mg/kg/day), the latter based on the above equivocal kidney finding. This study justifies dose levels used for the primary study. No DPR worksheet. Aldous, 6/5/07.

### **Rat Subacute Dietary Toxicity Study**

0138, 228832; "Cyclic Ketoenols BSN 3457, BSN 2342, FHN 7504, FHN 8330 Subacute Exploratory Toxicity Studies in Rats (Application by Feed Over 4 Weeks)" (Krotlinger, F. And Mihail, F., Bayer HealthCare AG, PH-GDD-Toxicology, Wuppertal, Germany, Study No. T 0061869 (Report No. MO-02-003395), 02/13/98). This study was submitted without providing details on the testing protocols used and without analyses of the test compounds. No lot numbers and purity information were provided for the 4 unidentified test articles used, cyclic ketoenols 1. BSN 3457, 2. BSN 2342, 3. FHN 7504, 4. FHN 8330. The test articles were mixed into the feed and each fed to 5 female Hsd/Win:WU rats per dose at dose levels of 500 and 5000 ppm (except for the BSN 2342 treated group where only the 5000 ppm dose level was used) for 4 weeks. One control group of 10 females was used. No mortalities occurred. No clinical signs were reported except for the BSN 2342 treated group at 5000 ppm where piloerection, pallor, decreased reactivity, and spastic gait were observed. Decreases in mean body weight were observed in the BSN 3457 and BSN 2342 treated groups at 5000 ppm. An

increase in mean relative liver weight was observed in the BSN 2342 treated group at 5000 ppm. Microscopic examination revealed slight to moderate cytoplasmic change in the liver of BSN 2342 treated group at 5000 ppm. Liver cell proliferation investigations revealed no treatment-related effects. NOEL (F) for FHN 7504 and FHN 8330 treated groups were determined to be 530.3 mg/kg/day (5000 ppm) and 501.8 mg/kg/day (5000 ppm), respectively, based on no effects at the highest dose test; NOEL (F) for the BSN 3457 treated group was determined to be 52.7 mg/kg/day (500 ppm) based on decreased mean body weight; NOEL (F) for the BSN 2342 treated group was not determined. **No adverse effects indicated.**  
**Supplemental data.** (Corlett, 09/14/07)

#### **Rat Subchronic Dietary Toxicity Study**

**\*\*53020-0139 228833** Wahle, B. S., "Technical grade BYI 08330: a subchronic toxicity testing study in the rat," Bayer CropScience LP, Stilwell, KS, June 1, 2005. Bayer Report # 201136. Groups of 10 Wistar Hanover - Crl:WI[Glx/BRL/Han]IGS BR rats/sex/group were dosed in diet for 13 weeks with Spirotetramat (BYI 08330), purity 96.5%, in a standard dietary subchronic study at 0, 150, 600, 2500, or 10000 ppm, equivalent to mean exposures of 8.9, 36, 148, or 616 mg/kg/day in males, or 11.4, 46, 188, or 752 mg/kg/day in females. Parallel controls and 10000 ppm groups (10/sex/group) were treated on the same regimen followed by a 4-wk recovery period. NOEL = 2500 ppm, based on 8% body weight decrements (males), testicular degeneration and/or vacuolization, epididymal abnormal spermatozoa and/or hypospermia, and accumulations of alveolar macrophages (both sexes). Reproductive toxicity is a possible adverse effect, however such was evident only at a very high dose level. The 4-wk recovery period appeared to eliminate lung pathology, however there was only partial recovery of testicular and epididymal histopathology. Study is acceptable. Aldous, 11/16/07.

#### **Dog 4-Week Dietary Toxicity Study**

53020-0171 228865 Eigenberg, D. A., "Technical Grade BYI 08830: A subacute toxicity feeding study in the beagle dog," Bayer CropScience LP, Stilwell, KS, 12/13/05. Bayer Report # 201012. Two beagles/sex/group were dosed in diet for 4 weeks with 0, 100, 400, 1600 or 6400 ppm of Spirotetramat (BYI 08330), Batch # NLL6425-9, purity 96.5%. Estimated achieved dose levels were 3, 13, 42, and 104 mg/kg/day in treated males, and 3, 12, 70, and 127 mg/kg/day in treated females. NOEL = 100 ppm, based on dose-related reductions in  $T_4$  levels in males at days 7 and 23, and in females on day 7. Often TSH and/or  $T_3$  levels were quite reduced at 6400 ppm. There was weaker evidence of treatment-related reduction of  $T_3$  in 400 to 1600 ppm males. All 6400 ppm dogs appeared "thin" at clinical observations. High dose males lost 1.5 kg by day 21, and high dose females lost 1.1 kg in this period, compared to body weight gains of several hundred grams in all other groups. Average food consumption (g/dog/day) was greatly decreased in 1600 and 6400 ppm males (to 66% and 35% of control intake, respectively), and in 6400 ppm females (to 50% of controls). Involved thymus was the only remarkable histopathology finding: both 6400 females and one 6400 male were involved. Despite the changes in concentrations of thyroid-associated hormones, thyroids displayed no histopathology. Useful supplementary data, providing a basis for dose selection for the subchronic study. Aldous, 11/19/07.

#### **Dog Subchronic Dietary Toxicity Study**

**\*\*53020-0141 228835** Eigenberg, D. A., "Technical Grade BYI 08830: A 90-day subchronic toxicity feeding study in the beagle dog," Bayer CropScience LP, Stilwell, KS, May 9, 2005. Bayer Report # 201223. Four beagles/sex/group were dosed in diet for 3 months with 0, 150, 300, 1200 or 2500 ppm of Spirotetramat (BYI 08330), Lot/Batch # 08045/0014, purity 97.8%. [The high dose was initially 4000 ppm, but was reduced after 2 weeks to 2500 ppm due to excessive body weight losses in both sexes]. Estimated achieved dose levels were 5, 9, 33, and 81 mg/kg/day in treated males, and 6, 10, 32, and 72 mg/kg/day in treated females. NOEL = 150 ppm, based on reduced thyroxin ( $T_4$ ) levels in both sexes. NOAEL = 1200 ppm, based on

conspicuous depression of  $T_4$  levels in both sexes at all treatment intervals, and on significant reductions in  $T_3$  levels; both at 2500 ppm. High dose males and females, both of which lost significant body weight during the first two weeks of the study when dosed with 4000 ppm, did not show compensatory body weight recovery after dose levels of this group were lowered to 2500 ppm. Excessive reductions of  $T_4$  and  $T_3$  at 2500 ppm constitute a "possible adverse effect." Acceptable. Investigators considered the NOEL for  $T_4$  to be 300 ppm: possible rebuttal to DPR NOEL placement based on  $T_4$  levels should include assay methodology, whether free or total hormones were assayed, and comparative literature values. Aldous 11/16/07.

#### **Rat Repeated Dosing 28-Day Dermal Toxicity Study**

0142, 228836; "A Subacute Dermal Toxicity Study in the Rat with BYI 08330" (Eigenberg, D.A., Bayer Crop Science LP, Stilwell, KS, Report No. 201505, Study No. 05-S22-YC, 06/20/06). 870.3200. Technical grade BYI 08330 (Batch No. 08045/0014, purity = 97.6-98.5%), moistened with deionized water, was applied to the clipped skin of 10 Wistar Hanover rats per sex per dose at dose levels of 0 (deionized water), 100, 300, or 1000 mg/kg/day for 6 hours per day 5 consecutive days per week for 4 weeks. No treatment-related mortalities occurred. No treatment-related clinical signs were observed. Examination of body weight data revealed no treatment-related effects. Serum chemistry and hematology revealed no treatment-related effects. Organ weight data revealed no treatment-related effects. Macroscopic and microscopic examinations revealed no treatment-related abnormalities. **No adverse effects.** NOEL (M/F, systemic and skin effects) = 1000 mg/kg/day (based on no effects at the highest dose tested). **Acceptable.** (Corlett, 09/11/07)

#### **Metabolites or Other Analogs of Spirotetramat:**

#### **Rat 10-Day Oral Toxicity Study**

0198; 228892; "BYI 08330-Enol: Exploratory 10-Day Toxicity Study in the Rat by Gavage" (Tinwell, H., Bayer CropScience, Sophia Antipolis Cedex, France, Report of Study SA 05323, 06/30/06). BYI 08330-enol (Batch No. 692-101-09-0005, purity = 96.8%), suspended in 0.5% methylcellulose in distilled water, was administered by gavage daily to 3 male Wistar (Rj; WI(IOPS HAN)) rats at a dose level of 800 mg/kg/day for 10 days. No mortalities occurred. No clinical signs were observed. A reduction in mean body weight gain was observed. NOEL (M) not determined. **Supplemental study** ((1) the test article, BYI 08330-enol, is a rat metabolite of the active ingredient BYI 08330, (2) only male animals were used, (3) only 3 animals were used, (4) only 1 dose level was used, and (5) the animals were treated for only 10 days). (Corlett, 09/18/07)

#### **METABOLISM**

53020-0107 228801 Klempner, A., "[Azaspirodecenyl-3- $^{14}$ C]BYI 08330: adsorption, distribution, excretion and metabolism in the rat," Bayer CropScience AG, Monheim am Rhein, Germany, 2/15/06. Bayer Study No. MEF-048/04. Title refers to absorption rather than adsorption. Groups of 4 Wistar Hsd/Cpb: WU rats/sex/group were dosed with Azaspirodecenyl-3- $^{14}$ C [i.e. spirotetramat with label in the #3 position of the spirodecenyl ring] with single gavage doses (in 0.5% aq. Tragacanth®, approximately 10 ml/kg) at 2 or 100 mg/kg. Similar groups were dosed with unlabeled spirotetramat for 14 days at 2 mg/kg/day, followed by treatment with 2 mg/kg of labeled spirotetramat. Pre-treatment with spirotetramat had no influence on outcomes. All groups were evaluated for excretion patterns (urine and feces) and plasma levels over 48 hr, at which time rats were sacrificed for evaluation of tissues. Investigators analyzed pharmacokinetic patterns and evaluated all major metabolites. Label was quickly and efficiently absorbed, with calculated plasma  $T_{max} \leq 2$  hr in all groups, and with rapid phase 1 elimination in all groups. All groups cleared at least 96% of administered dose during the first 24 hr after dosing. From 89% to 98% of label was excreted in urine. Fecal elimination was 5-7% of dose in low dose males, 11% in high dose males, and 2-3% of dose in all female groups. Tissue

residues at 48 hr termination were very small. In all cases, the dominant urinary metabolite was the -enol (a single cleavage at the 4-yl ethyl ester), constituting 64-66% of dose in low dose males, 51% of dose in high dose males, and 80-86% of dose in all females. The only other significant metabolite was the -desmethyl-enol (-enol with additional loss of methyl from the methoxy group). The latter constituted 22-24% of dose in low dose males, 4-5% in low dose females, and 32% and 9% respectively in high dose males and females. Other metabolites were minor subsequent degradation products of these two species. This is the primary metabolic disposition study (out of at least 6 related rat disposition studies), and is valid in its scope. Aldous, Dec. 5, 2007.

53020-0161 228855 Klempner, A., "[Azaspirodecenyl-3-<sup>14</sup>C]BYI 08330: depletion of residues and metabolites in plasma, urine, liver, kidney and testis of the male rat," Bayer CropScience AG, Monheim am Rhein, Germany, Aug. 11, 2006. Bayer CropScience AG Report #: MEF-06/328. Groups of 4 male Wistar Hsd/Cpb: WU rats/group were dosed with Azaspirodecenyl-3-<sup>14</sup>C [i.e. spirotetramat with label in the #3 position of the spirodecenyl ring] with single gavage doses (in 0.5% aq. Tragacanth®, approximately 10 ml/kg) at 2 or 1000 mg/kg. This study was performed to evaluate effects of a very high dose on disposition of spirotetramat compared to the earlier study employing 2 and 100 mg/kg (see Record No. 228801). Uptake and clearance was slow at 1000 mg/kg compared with the rapid absorption observed at ≤ 100 mg/kg. The 1000 mg/kg group excreted only 27% of dose in urine and 18% in feces: about 47% of dose remained in the g.i. tract (with contents) as of 24 hr after dosing. This suggests that active processes such as membrane transport and/or metabolism can be saturable at very high dose levels. As a result, the percent of dose remaining in plasma and tissues at 24 hr after dosing was at least 10 x higher after the high dose compared to the low dose. Useful supplementary data. Aldous, Dec. 5, 2007.

53020-0162 228856 Klempner, A., "[Azaspirodecenyl-3-<sup>14</sup>C]BYI 08330: distribution of the total radioactivity in male and female rats determined by quantitative whole body autoradiography (QWBA) including determination of the total radioactivity in excreta and exhaled <sup>14</sup>CO<sub>2</sub>," Bayer CropScience AG, Monheim am Rhein, Germany, 2/21/06. Bayer CropScience AG Report #: MEF-06/15. Eight Wistar Hsd/Cpb: WU rats/sex/group were dosed with Azaspirodecenyl-3-<sup>14</sup>C [i.e. spirotetramat with label in the #3 position of the spirodecenyl ring] with single gavage doses (in 0.5% aq. Tragacanth®, approximately 10 ml/kg) at 3 mg/kg. One rat/sex was sacrificed at 1, 4, 8, 24, 48, 72, 120, or 168 hr post-treatment. One control rat/sex was dosed with non-radiolabeled spirotetramat at 3 mg/kg. Expired air was scrubbed by ethanolamine/ethanol traps for rats scheduled for ≥24 hr exposure to assess <sup>14</sup>CO<sub>2</sub>. Urine and feces were collected at intervals. At sacrifice, each rat was stretched over a template and quick-frozen. Up to 5 sagittal sections per rat were cut, and surfaces were developed on imaging plates, providing counts for 24 organs/tissues. <sup>14</sup>C-labeled blood samples covering a range of <sup>14</sup>C concentrations served as standards for comparison. No more than 0.004% of administered dose was obtained in expired air during the first 48 hr after treatment. Radioactive residues dropped rapidly in males by 24 hr, at which time residues were quantifiable only in liver, renal cortex, and renal medulla. Male renal tissues were below limit of detection by 48 hr. There was still meager but quantifiable label remaining in the 72-hr male liver. By 168 hr, liver label was below the limit of detection. Female tissue label was below limit of detection in all tissues by 24 hr post-dosing. Valid supplementary data, confirming the rapid clearance of label from tissues. Aldous, no worksheet, 11/28/07.

53020-0165 228859 Totis, M., "[Azaspirodecenyl-3-<sup>14</sup>C]BYI 08330: comparison of the *in vitro* metabolism in Liverbeads™ from male rat, mouse and human," Bayer CropScience, Sophia Antipolis, France, 6 July 2006. Investigators found that hepatocytes of all three species produced primarily the enol metabolite and no parent compound remained following incubation for 4 hrs at 50 μM or 520 μM, consistent with rat *in vivo* studies previously conducted. At low dose levels (50 μM), rat hepatocytes produced 87% enol, 7% desmethyl-enol, 3% keto-hydroxy,

4% enol alcohol, and no enol-glucuronide; mouse hepatocytes produced 66% enol, 1% desmethyl-enol, 2% keto-hydroxy, 1% enol alcohol, and 30% enol-glucuronide; and human hepatocytes produced 92% enol, 1% desmethyl-enol, 0% keto-hydroxy, 0% enol alcohol, and 6% enol-glucuronide. At the maximum obtainable level (520  $\mu$ M), nearly all label was in the enol form in all species. These metabolites were identified based on HPLC elution patterns (UV and radiometric detection), and by MS. Of these metabolites, only the identity of a minor metabolite, enol alcohol, could not be confirmed with certainty (although the elution fraction contained an appropriate MS peak for the molecular ion). It appears that humans would be unlikely to produce metabolic products of greater concern than those found in rats. Aldous, useful supplementary data, no DPR worksheet, 11/28/07.

53020-0199 228893 Klempner, A., "[Azaspirodecenyl-3- $^{14}$ C]BYI 08330-enol-glucoside supplemental study: absorption, distribution, excretion and metabolism in the rat," Bayer CropScience AG, Monheim am Rhein, Germany, 2/09/06. Bayer CropScience AG Report #: MEF-06/006. A single male rat was dosed orally with the enol-glucoside of spirotetramat (99% radiochemical purity) at 0.1 mg/kg. This residue is found in some vegetables. Plasma, urine, and feces were collected for 48 hr, at which time the rat was sacrificed and residues in the carcass and g.i. tract were assessed. Highest plasma concentrations were observed at 6 to 8 hr after dosing. Plasma concentrations 48 hr after dosing were reduced to about 0.5% of peak levels (p. 40). Excretion in urine (53% of administered dose by 48 hr) and feces (44% of administered dose by 48 hr) was rapid: about 98% of excretion by both routes was complete by 24 hr (p. 43). About 1.2% of administered dose was found in or on the carcass at sacrifice. The predominant urinary metabolite was the enol (47% of administered dose). Minor urinary metabolites were the desmethyl-enol (4.6% of administered dose) and the administered article (enol-glucoside) 0.5% of administered dose. In feces, 16% of administered dose was found as the enol, 21% as parent enol-glucoside, 3.1% as the keto-hydroxy metabolite, and 0.6% as the desmethyl-enol (p. 45). Although this study used only elution profiles for compound identification, previous studies by this author give adequate evidence that reported metabolites were actually observed. These valid supplementary data do not indicate concerns about consumption of this plant metabolites in the diet. No DPR worksheet. Aldous, 11/28/07.

53020-0193 228887 Klempner, A., "[Azaspirodecenyl-3- $^{14}$ C]BYI 08330-ketohydroxy: absorption, distribution, excretion and metabolism in the rat," Bayer CropScience AG, Monheim am Rhein, Germany, 2/20/06. Bayer CropScience AG Report #: MEF-06/007. A group of 4 male rats was orally dosed with 2 mg/kg ketohydroxy metabolite of spirotetramat, which is found in some fruit and vegetable crops, and which is a minor rat metabolite of spirotetramat. Plasma, urine, and feces were collected for 48 hr, at which time the rats were sacrificed and residues in various organs including the g.i. tract were assessed. Highest plasma concentrations were observed at about 40 minutes after dosing. Less than 1% of plasma peak level remained at 24 hr (p. 50). About 54% of administered dose was excreted in urine, and 40% in feces by 24 hr (p. 57). Only about 0.2% of administered radioactivity was found in the body at 48 hr (p. 52). Specific activities in all organs evaluated at 48 hr were less than that of liver (p. 54). Administered ketohydroxy metabolite was not found in urine, and comprised less than 1% of administered dose in feces (p. 57). There were many separable peaks for urinary and fecal metabolites, and virtually all involved a demethylation of the test article. Investigators did not seek to fully characterize the metabolites, however they provided LC-MS and LC-MS/MS profiles so that the presence but not the locations of substituents were reported. About 34% of administered dose were metabolites containing one additional oxygen, about 28% of administered dose carried 2 additional oxygens, and 3% of administered dose contained 3 additional oxygens. Some of these metabolites had lost two hydrogens. Small fractions of metabolites were sulfate or glucuronide conjugates (p. 57). These valid supplementary data do not indicate concerns about consumption of this plant metabolite in the diet. No DPR worksheet. Aldous, 11/27/07.

**STABILITY STUDIES OF SPIROTETRAMAT IN RODENT RATION**

53020-0172 228866 Jensen, T. L., "The homogeneity and stability of BYI Technical in rodent ration," Bayer CropScience LP, Stilwell, KS, 5/11/05. Spirotetramat (96.5% purity) was prepared at 70, 150, or 10000 ppm. Homogeneity was indicated by CV's of 3.2 to 5.5%, with 9 samples per concentration level. Stability was indicated at freezer temperature, as there were no evident losses up to the maximum duration of 28 days at any concentration. Stability at room temperature was indicated by all values being in the range of 85-117% of nominal over 7 days, with no systematic change in concentration. These stability data support rodent studies in these concentration ranges. Aldous, 6/1/07 (no worksheet).

53020-0173 228867 Jensen, T. L., "A revised homogeneity and stability of BYI Technical in rodent ration," Bayer CropScience LP, Stilwell, KS, 10/4/05. To correspond to slightly different dose levels than in Record No. 228866, above, spirotetramat (97.5% purity) was prepared at 70 and 12000 ppm. Homogeneity was indicated by CV's of 2.1 to 3.8%, with 9 samples per concentration level. Stability was demonstrated at freezer temperature, as there were no evident losses up to 29 days or 32 days, the longest durations evaluated for 12000 and 70 ppm, respectively. Stability at room temperature was indicated by no losses up to the maximum time tested (7 days). This study confirms satisfactory homogeneity and stability at a slightly different concentration range from the above study. Aldous, 6/1/07 (no worksheet).