I. DATA GAP STATUS

Chronic toxicity, rat: No data gap, no adverse effect
Chronic toxicity, dog: Not required at this time
Oncogenicity, rat: No data gap, no adverse effect
Oncogenicity, mouse: No data gap, possible adverse effect (not tumors)
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 261364 (Document No. 53162-0091) were examined. This includes all relevant studies indexed by DPR as of 5/21/2012.

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: t20120808.wpd
Revised by Name, Date (original by Aldous, 8/8/2012)
II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

COMBINED, RAT

**53162-0021  261212  Schladt, L. and U. Deschl, “Bayticol P: Combined study on chronic
toxicity and carcinogenicity in Wistar rats. Dietary administration over 2 years with dose-
adjustment,” Bayer AG, Wuppertal, Germany, 6/16/99. Bayer ID # 19360. Groups of 50 Wistar
[Hsd Cpb:WU] rats were dosed in diets adjusted weekly to provide 0, 0.7, 2, and 4 mg/kg/day of
Bayticol P (Flumethrin), purity 93.5-95.7%, in a 2-yr oncogenicity study. An additional
10/sex/group were fed at these dose levels for a 1-yr chronic study component. Initially the
highest dose level was 6 mg/kg/day, however excessive mortalities due to skin lesions incidental
to pruritis necessitated a step-down from 6 to 4 mg/kg/day after 17 weeks of treatment. Another
adjustment to study design was that the first 10 rats/sex to die in the highest dose group were
designated as chronic study rats, to preserve sufficient numbers for a meaningful lifetime
oncogenicity evaluation. Since over 10/sex died during the first year at 6 to 4 mg/kg/day, there
were no survivors in that group at 1-yr scheduled sacrifice for terminal hematology, clinical
chemistry, ophthalmology, etc. Nevertheless, survival for the oncogenicity study was
comparable between groups for both sexes by termination, and the study is valid for evaluation
of all essential elements. NOEL in males is slightly under 0.7 mg/kg/day, based on 2/50 lifetime
exposure males at that dose showing skin changes plausibly associated with scratching behavior
from pruritis. NOEL in females is 0.7 mg/kg/day. Skin changes (usually piloerection,
sometimes accompanied by hair loss) were sharply dose-related in the range of 2-4 mg/kg/day in
both sexes. An overall summary of percentages of affected rats was 0, 3, 17, and 70% affected
in males, and 0, 0, 15, and 43% in females: such changes thus defined the NOEL’s for both
sexes. Chronic inflammation and ulceration were markedly elevated in most 6 to 4 mg/kg/day
chronic study males and females, and such pathology was considered to be cause of premature
death or moribund sacrifice in most cases. These lesions were not elevated in 0.7 or 2 mg/kg/day
rats of either sex in 1-yr chronic or lifetime study rats. Most characteristic treatment-related
systemic histopathology was associated with the skin lesions: i.e. extramedullary hematopoiesis
in spleen and liver. Body weights were significantly reduced in high dose males, but not in other
groups. A modestly increased vacuolation of the adrenal cortex in males only at or over 2
mg/kg/day was possibly treatment-related in chronic study rats. Slight increases in skeletal
muscle myodegeneration and in severity of sciatic nerve fiber degeneration were observed in
lifetime study high dose males: both plausibly minor treatment effects. Study is acceptable, with
no adverse effects. Aldous, 7/26/12.

CHRONIC TOXICITY, RAT

See COMBINED, RAT above.

CHRONIC TOXICITY, DOG

Not required at this time.
ONCOGENICITY, RAT

See COMBINED, RAT above.

ONCOGENICITY, MOUSE

**53162-0023 261214** Wirnitzer, U. and H. Hartmann, “Bayticol P: oncogenicity study in CD-1 mice. (Dietary administration over 18 months).” Bayer AG, Wuppertal, Germany, 7/28/99. Bayer ID # 19383. Groups of 50 Crl:CD-1(ICR)BR mice/sex/group were dosed in diet with Bayticol P (Flumethrin), purity 93.5-93.8%, Batch 816458003, in an oncogenicity study at 0, 3, 15, or 30 ppm. An additional 10/sex were administered 1 ppm to provide a NOEL for skin irritation or associated sores. Mean achieved dose levels were 0.12, 0.39, 1.97 and 4.56 for increasing dose levels in males, and 0.15, 0.52, 2.54, and 4.95 for corresponding females. Absolute NOEL < 1 ppm: “skin changes” were observed in dose-related fashion in all treated groups. Such changes at 1 ppm were exclusively limited to red spots on the tail. These did not persist beyond 20 weeks into the study at 1 ppm. Most 3 ppm mice also showed only temporary changes in the tail, but a few had skin lesions on forward parts of the body, such as ears and neck: responses typical of higher dose groups. The most characteristic skin lesions at 15 to 30 ppm in both sexes were missing pinnae (external ears) as clinical signs and associated histopathology findings of epidermal hyperplasia, inflammation, and ulceration of the pinnae. Similar findings of the neck and/or back at 3 ppm and above were slightly less common than ear changes. Increased hematopoiesis such as in spleen and bone marrow were among the most common secondary findings. Survival was reduced at 30 ppm in both sexes. Acceptable. Skin sensations which led to scratching and subsequent pathology are “possible adverse effects,” however most species, including rats and domestic animals for which this compound is used as a topical treatment, are much less sensitive to dermal effects. Aldous, 6/25/12.

**53162-0024 261215** Leser, K. H. and A. Popp “Bayticol P: Report on two dose-range-finding studies in CD-1 mice: (Administration in the food over 3 months).” Bayer AG, Wuppertal, Germany, 1/27/98. Bayer ID # 18255. These studies formed the basis of dose selection for the oncogenicity study above. Groups of 10 Crl:CD-1(ICR)BR mice/sex/group were dosed in diet with Bayticol P (Flumethrin), purity 94.4-95.1%, in two successive subchronic studies. Dose levels in the first study were 0, 60, 120, 240, and 480 ppm. Deaths by termination (sexes combined) in that study were 0, 4, 7, 12, and 20 for controls through increasing dose levels, respectively. Skin changes and associated inflammation and wounds were observed in all treated groups. The second study tested 0, 5, and 10 ppm. Treated groups had minor skin changes, but results were otherwise unremarkable. Dose range for the oncogenicity study was well-founded, based on these results. No DPR worksheet for these pilot studies, as they are unlikely to provide unique endpoints of toxicity. Aldous, 1/18/12.

REPRODUCTION, RAT

**53162-0027 261219** Eiben, R., “Flumethrin: Two-generation reproduction study in Wistar rats (Administration by gavage),” Bayer HealthCare AG, Wuppertal, Germany, Nov. 10, 2008. Bayer Report ID: AD-D-ID# 32775. Groups of 25 Wistar [Crl: (Wi)WU BR] rats/sex/group were dosed by gavage (5 ml/kg corn oil vehicle) daily with Flumethrin, Batch No. KP03HHE04,
95.8% purity at 0, 0.5, 1, and 3 mg/kg/day. Treatment was continuous through 10-week pre-mating, mating, and (for females) lactation, with selected F1 parents dosed from PND 28 weaning onwards for the second generation. Parental systemic toxicity NOEL = 1 mg/kg/day, based on diminished body weight in F0 and F1 males during pre-mating, and in F0 and F1 females during gestation days 14-20 as well as during lactation days 0-4. Parental reproductive effects NOEL = 3 mg/kg/day (no effect noted). Offspring viability and growth NOEL = 1 mg/kg/day, based on marked increases in neonatal deaths and an average of 10% decrement in mean pup weights at lactation day 21 in both generations at 3 mg/kg/day. Associated clinical observations in high dose pups were presence of or increased numbers of “no milk spots,” “relatively small,” and “thin;” suggestive of diminished maternal care. Study is acceptable, with no adverse effects. Aldous, August 8, 2012.

53162-0045  261237  Krebber, R. and J. Hoffend, “Determination of flumethrin in rat plasma within the scope of the toxicological study T9073333,” Bayer CropScience AG, Monheim am Rhein, Germany, 4/25/07. Bayer Study No. 30971. This brief record reported plasma flumethrin concentrations in F0 rats sampled at 1-7 hrs after daily dosing on study days 38 or 39. Peak concentrations in both sexes at all dose levels peaked at 4 hrs post dose. Achieved peak levels in males at 0.5, 1.0, and 3.0 mg/kg/day were 171, 339, and 508 µg/L. Corresponding peak levels in females were 105, 260, and 492 µg/L. These biokinetics data relate to the associated reproduction study and other rat studies. Note that peak levels at 3 mg/kg/day were much less than a three-fold increase over the 1 mg/kg/day group. Aldous, no worksheet, 4/16/2012.

53162-0029  261221  Eiben, R., “Flumethrin (Project: PNR 1395): Exploratory subacute oral toxicity study in rats (Pilot study for a two-generation study with a 4 weeks administration via gavage),” Bayer HealthCare AG, Wuppertal, Germany, 11/14/06. Bayer Report # 30322. This study tested flumethrin at 0, 5, 7.5, and 10 mg/kg/day (gavage, in corn oil) in Wistar rats (5/sex/group). Rats were about 5 weeks of age at onset of dosing, and were not mated. Observations were limited to clinical signs, food consumption and body weight, and gross necropsy (with organ weights). Investigators reported reduced food and water consumption, reduced body weights, reduced absolute and relative spleen and thymus weights, and increased salivation: each generally at 7.5 and 10 mg/kg/day. Useul supplementary data: no DPR worksheet. Aldous, Dec. 7, 2011.

53162-0030  261222  Eiben, R., “Flumethrin (Project: PNR 1395): Exploratory subchronic oral toxicity study in rats (Pilot study for a two-generation study with a 19-weeks administration via gavage),” Bayer HealthCare AG, Wuppertal, Germany, 11/21/06. Bayer Report # 30686. This study tested flumethrin at initial dose levels of 0, 0.08, 0.4, and 2.0 mg/kg/day (gavage, in corn oil) in Wistar rats (5/sex/group). No toxicity was evident, so dose levels were changed to 0, 3, 4, and 5 mg/kg/day for days 80-134. Rats were then mated 1:1, and females were maintained through lactation day 4 to 6 to assess early lactation period toxicity. Body weights were marginally reduced at 4-5 mg/kg/day in males, and during gestation in 4-5 mg/kg/day females. Common clinical signs in 4-5 mg/kg/day females were “reduced motility” and “increased salivation.” Neonatal mortality was high: only 1/4 high-dose litters had living pups at day 4. All of these litters reported “little milk / no milk spot,” as did also 2/3 of 4 mg/kg/day litters. Limited kinetic data indicate that maximal plasma concentration was at about 2-4 hrs after gavage dosing. Data support dose selection for the definitive reproduction study (Record No. 261219). No DPR review for this pilot study. Aldous, 12/15/11.
This is a kinetics study performed as part of Record No. 261222, above, which data were entirely contained in that record. Aldous, 12/15/11.

**53162-0028 261222** Dotti, A., J. Kinder, K. Biedermann, H. Luetkemeier, J. Wright, and Ch. Terrier, “Bay Vq 1950: Multiple generation reproduction study in rats,” RCC, Research and Consulting Company AG and RCC Umwelchemeie AG, Itingen, Switzerland, 2/18/92. Bayer ID: AD-D-ID# 13252. Wistar rats were dosed in diet continuously for 2 generations, 2 mating periods per generation, with pre-mating exposures of 84 days for F0 parents, and 105 days for F1 parents. Test article was Bay Vq 1950: 45.6% a.i. (flumethrin), and 54.4% carrier (Aerosil 200), at 0, 1, 5, or 50 ppm. Estimated intakes of F0 parents during the 12th study week were 0.1, 0.3, and 3.0 mg/kg/day for males, and 0.1, 0.3, and 3.5 mg/kg/day for females of respective groups. Corresponding F1 parental pre-mating food consumption was comparable. N = 30 pairs for F0 and 26 pairs for F1. Design did not include tracking estrous state of females in late lactation, nor attainment of vaginal opening or preputial separation, nor were sperm parameters assessed. Parental systemic toxicity NOEL = 5 ppm, based on (1) sores due to scratching resulting from skin irritation in 15/56 of parental males (F0 plus F1) and 2/56 females, (2) decreased (21-41%) food consumption during lactation in all littering periods, (3) markedly reduced body weights of F1 parents (influenced in part by growth delays as pups), and (4) modestly decreased body weights and food consumption in either sex at times during the study. Parental reproductive effects NOEL = 50 ppm (no treatment effects). Offspring viability and growth NOEL = 5 ppm, based on large early post-natal losses (19-43% of live-born pups), and on consistent decrements in pup growth (an average of 25% pup body weight decrement over the four littering periods). Acceptable, however a more recent study has a more modern design and a better choice of dose levels and route of exposure (see DPR Document No. 53162-0027, Record No. 261219). No adverse effects. Aldous, August 8, 2012.

### DEVELOPMENTAL TOXICITY, RAT

**53162-0025 261216** Klaus, A.-M., “Bayticol P: Developmental toxicity study in rats after oral administration,” Bayer AG, Wuppertal, 1/13/99. Report ID: AD-D-ID# 18968. Groups of 27 mated Wistar [Hsd Cpb:WU] females were dosed by gavage (in 2 ml/kg corn oil) with Flumethrin (Bayticol P: purity 93.8%) at 0, 0.75, 2, or 5 mg/kg/day during gestation days 6-19 in a guideline developmental toxicity study. At gestation day 20 termination, all fetuses received external examinations. Nearly one-half per litter were examined by modified Wilson technique, and the balance were processed for skeletal and cartilage effects. There was a significant, dose-related decrease in food consumption at 2-5 mg/kg/day, and a significant body weight gain decrement at 5 mg/kg/day. The most prevalent clinical sign was salivation, affecting all high dose females. Also, six 2 mg/kg/day females showed salivation (usually “slight” degree, and in all these cases observed on only one day). The most common signs, elevated only in high dose dams, included wounded ears (from pruritis and subsequent scratching), and reduced feces. Maternal NOEL = 0.75 mg/kg/day, based on decreased food consumption and clinical signs of salivation. Developmental NOEL = 2 mg/kg/day, based on 23% decrement in fetal body weight, and on ossification delays in several sites. Dysplasia of forelimb bones (most commonly scapula) was non-significantly elevated in high dose fetuses [observed in 1 control fetus, vs. 6 high dose fetuses (3 litters)]; this was not statistically significant and was within historical range, and appears to be incidental. Study is acceptable, with no adverse effects. Aldous, July 2, 2012.
DEVELOPMENTAL TOXICITY, RABBIT

**53162-0026 261217 Langewische, F., “Flumethrin: Developmental toxicity study in rabbits after oral administration,” Bayer Schering Pharma AG, Wuppertal, Germany, 10/28/09. Report ID No. AD-D-ID# 35286. Groups of naturally bred 22 CHBB:HM does/group were dosed by gavage with Flumethrin, 95.8% purity, Batch No. KP03HHE04, at 0, 0.5, 1.5, or 4.5 mg/kg/day on gestation days 6-28 in a developmental toxicity study. Maternal NOEL = 1.5 mg/kg/day, based on 4 abortions, encrusted wounds of throat and/or forelimbs in 4 does, decreased water consumption (associated with signs of dark-discolored urine and decreased urination), decreased food consumption, decreased body weight, and diarrhea. Five high dose dams had course-grained placentae, compared to none in other groups. Developmental NOEL = 1.5 mg/kg/day, based on increased late resorptions and decreased fetal body weights (both plausibly related to maternal toxicity). Study is acceptable, with no adverse effects. Aldous, July 5, 2012.

GENE MUTATION

**53162-0035 261227 Herbold, A., “Flumethrin: Salmonella/microsome test, plate incorporation and preincubation method,” Bayer HealthCare AG, Wuppertal, Germany, 11/23/06. Bayer ID # 30687. Salmonella typhimurium strains TA 1535, TA 100, TA 1537, TA 98, and TA 102 were tested with Flumethrin, 95.8% purity, Batch No. KP03HHE04 at 5000, 1581, 500, 158, 50, and 16 μg/plate in DMSO in a plate incorporation study with two trials, one plate incorporation test and one by preincubation for 20 minutes at 37 °C prior to plating at 37 °C for 48 hrs, N = 3 in all cases. Flumethrin was marginally cytotoxic: bacterial titers were statistically significantly reduced with strain TA 1535 at 5000 μg/plate with plate incorporation, but not in other tests, and there was a statistically significant decrease in revertants at 5000 μg/plate with TA 98 with S-9 in the plate incorporation test only. There was precipitation at 5000 ppm flumethrin, but not at lower levels. There were no increases in revertants. Study is acceptable, and is negative for mutagenicity. Aldous, Aug. 6, 2012.

53162-0033 261225 Gahlmann, R., “Flumethrin: Salmonella/microsome test,” Bayer AG, Wuppertal, Germany, 10/19/93. Bayer ID # 14173. Salmonella typhimurium strains TA 1535, TA 100, TA 1537, and TA 98 were subject to concentrations of 5000, 1000, 200, 40, and 8 μg/plate of Flumethrin (purity 94.6%, Batch 898230001) in DMSO in a plate incorporation study with two trials, and four samples per level. Flumethrin was not cytotoxic at any dose tested. There was precipitation at 5000 ppm flumethrin, but not at lower levels. There were no increases in revertants. This study is designated as supplementary, because of the lack of a fifth strain such as Salmonella typhimurium TA 102 or E. coli WP2 uvrA. There is a more recent study, DPR Record No. 261227 (Bayer study 30687), which would supersede this study. Aldous, 4/17/12.

53162-0034 261226 Gahlmann, R., “Flumethrin: Salmonella/microsome test, special study,” Bayer AG, Wuppertal, Germany, 10/19/93. Bayer ID # 14174 “Flumethrin: Salmonella/microsome test,” Bayer AG, Wuppertal, Germany, 10/19/93. Bayer ID # 14173. This was an adjunct to DPR Record No. 261225 (Bayer ID # 14173), conducted by the same laboratory as the former, but extending the dose range to 7500, 10000, 12500, and 15000 μg/plate of Flumethrin (purity 94.6%, Batch 898230001) in DMSO for 48 hrs at 37 °C in a plate incorporation study with two trials, and four samples per level. Flumethrin was not cytotoxic at
any dose tested. There was precipitation at 7500 ppm flumethrin and above. There were no increases in revertants. This study is designated as supplementary, as was Record No. 261225, because of the lack of a fifth strain such as Salmonella typhimurium TA 102 or E. coli WP2 uvrA. Aldous, Aug. 6, 2012.

**53162-0036 261228** Brendler-Schwaab, S., “Flumethrin: Mutagenicity study for the detection of induced forward mutations in the V79-HPRT assay in vitro,” Bayer AG, Wuppertal, Germany, 7/14/95. Bayer ID # 15461. Flumethrin, purity 95.1%, Batch 898230901 was evaluated at 6.25, 12.5, 25, 50, 75, and 100 µg/ml in two tests with and two tests without S-9. There were duplicate replicates at each level per test for flumethrin, for untreated and vehicle (DMSO) controls, and for (-S-9, +S-9) positive controls [EMS, 900 µg/ml; and DMBA, 20 µg/ml], which were effective. Concentrations ≥ 100 µg/ml caused precipitation, with or without S-9. No cytotoxicity was evident up to 200 µg/ml in the toxicity trial. There was no treatment-related increase in mutant colonies [negative with and without S-9]. Acceptable. Aldous, 4/18/12.

**53162-0039 261231** Entian, G., “Flumethrin: V79/HPRT in vitro for the detection of induced forward mutations,” Bayer HealthCare AG, Wuppertal, Germany, 6/20/07. Bayer ID # 31489. Flumethrin [95.8% purity, Batch No. KP03HHE04] was evaluated at 6, 12, 24, 48, 96, and 192 µg/ml in two tests with S-9 and two tests without S-9. There were duplicate replicates at each level per test for flumethrin, for untreated and vehicle (DMSO) controls, and for (-S-9, +S-9) positive controls [EMS, 900 µg/ml; and DMBA, 20 µg/ml]: both functional. Concentrations ≥ 96 µg/ml caused precipitation, with or without S-9. No cytotoxicity was evident up to 192 µg/ml. Flumethrin did not cause increased mutant colonies [negative with and without S-9]. Acceptable. Aldous, 4/18/12.

**53162-0037 261229** Thum, M., “Flumethrin: in vitro chromosomal aberration test with Chinese hamster V79 cells,” Bayer HealthCare AG, Wuppertal, Germany, 6/16/2007. Bayer ID # 31492. V79 cells were exposed to Flumethrin [95.8% purity, Batch No. KP03HHE04] with or without S-9 at 0 (DMSO vehicle), 25, 50, and 100 µg/ml for a 4 hr exposure; harvest at 18 hrs. Associated positive controls were mitomycin C, 0.1 µg/ml (without S-9) and cyclophosphamide 2.0 µg/ml (with S-9). Additional tests without S-9 were conducted at the above flumethrin dose levels with an 18-hr exposure and harvest at 18 hrs. Flumethrin was additionally tested with or without S-9 at 100 µg/ml for a 4 hr exposure, with harvest at 30 hrs. In all cases, flumethrin did not elicit chromosomal aberrations. Positive controls were functional. There were no effects on polyploidy. Acceptable, with no adverse effects. Aldous, 4/18/2012.

**53162-0038 261230** Herbold, B., “Flumethrin: in vitro mammalian chromosome aberration test with Chinese hamster V79 cells,” Bayer AG, Wuppertal, Germany, 11/22/95. Bayer ID # 16145, also designated No. 74691. V79 cells were exposed to Flumethrin, purity 95.1%, Batch 898230901 for 4 hrs, with harvest at 18 hrs, with or without S-9 activation, at 10, 70, and 125 µg/ml [2 replicates prepared per treatment and time combination, with 100 metaphases counted per paired replicate]. In addition, 125 µg/ml was applied for a 4 hr exposure, followed by harvest at 30 hrs (with and without S-9). Findings were negative except for 125 µg/ml flumethrin with S-9 in the primary test, which had a value above the historical range and
statistically significant compared to the concurrent control. A subsequent test was performed with dose levels of 75, 100, and 150 µg/ml for a 4-hr exposure with S-9, and 18-hr harvest. The latter study did not corroborate the significant finding of the first trial. Untreated and vehicle (DMSO) controls were included in all tests, and positive controls were included where relevant, and were functional. The study is acceptable and negative for clastogenicity. Aldous, 4/19/12.

**53162-0040 261232 Herbold, B., “Flumethrin: micronucleus-test on the male mouse,” Bayer HealthCare AG, Wuppertal, Germany, April 12, 2007. Bayer ID # 30951. Five young adult male NMRI mice/group were dosed twice ip with flumethrin [95.8% purity, Batch No. KP03HHE04] at each of 3 dose levels: (2 x 125 mg/kg, 2 x 250 mg/kg, or 2 x 500 mg/kg). Five additional high dose mice were dosed as potential replacements. Treatments were 48 hrs and 24 hrs before sacrifice. Negative controls received 10 ml/kg corn oil on that schedule, and positive controls received cyclophosphamide (20 mg/kg) 24 hrs before sacrifice. Cells taken from bone marrow of the femurs were evaluated to count micronuclei per 2000 PCE’s (polychromatic erythrocytes), and also micronuclei per 2000 NCE’s (normochromatic erythrocytes). Ratios of NCE’s/PCE’s were taken to assess toxicity. Micronuclei counts per PCE were unaffected by flumethrin, but greatly increased by cyclophosphamide. Micronuclei per 2000 NCE’s were unaffected in flumethrin groups or in positive control mice. The numbers of NCE’s per 2000 PCE’s were elevated above contemporary controls in the highest flumethrin group, although 6/25 control groups in the 2005 negative control historical data exceeded that value. Investigators observed that this was consistent with a “relevant systemic exposure.” More importantly, the highest flumethrin dose elicited marked clinical signs, and 2/10 died. The study is acceptable, and negative for treatment effects on micronuclei. Aldous, 7/17/2012.

**53162-0041 261233 Herbold, B., “Flumethrin: micronucleus test on the mouse,” Bayer AG, Wuppertal, Germany, 3/23/95. Bayer ID # 15198. Five young adult NMRI mice/sex/group were dosed once ip with Flumethrin, purity 95.1%, Batch 898230901, at 1000 mg/kg. Flumethrin treatments were 16, 24, or 48 hrs before sacrifice. Negative controls received 10 ml/kg corn oil, and positive controls received cyclophosphamide (20 mg/kg), each 24 hrs before sacrifice. Cells taken from bone marrow of the femurs were evaluated to count micronuclei per 1000 polychromatic erythrocytes (PCE’s), and also micronuclei per 1000 normochromatic erythrocytes (NCE’s). Ratios of NCE’s/PCE’s were compared to assess toxicity. Micronuclei counts per 1000 PCE’s were unaffected by flumethrin. Cyclophosphamide was effective as a positive control. Micronuclei per 1000 NCE’s were unaffected in flumethrin groups or in positive control mice. The numbers of NCE’s per 1000 PCE’s in the 48-hr pre-treatment group were statistically significantly higher than concurrent controls, and this ratio was higher than in any of the 56 control studies completed between 1991 and 1993. Investigators judged (defensibly) that this was a toxicological response. Flumethrin at 1000 mg/kg elicited marked clinical signs, and 1/40 mice died. The study is acceptable, and negative for treatment effects on micronuclei. Aldous, 4/20/2012.

DNA DAMAGE

**53162-0042 261234 Brendler-Schwaab, S., “Flumethrin: test on unscheduled DNA synthesis in rat liver primary cell cultures in vitro,” Bayer AG, Wuppertal, Germany, Nov. 8, 1994. Bayer ID # 14867. Flumethrin, Batch 898 230 001, purity 94.6%, was applied at 0, 5, 10, 50, 100, 200, 300, and 500 µg/ml in the UDS test. Primary hepatocytes from young male Sprague-Dawley rats
were isolated, distributed to coverslips in culture dishes, treated with above flumethrin doses or with positive control (0.5 µg/ml 2-acetylaminofluorene) in the presence of ^3^H-thymidine under standard UDS conditions. There were 3 slides per treatment, with 50 cells examined per slide. There no readable slides at 500 µg/ml. Survival was 52.3% at 300 µg/ml. None of the flumethrin groups showed elevated net nuclear grain counts. Positive control was highly functional. Study is acceptable, with no adverse effects. Aldous, 7/17/2012.

**NEUROTOXICITY (rat)**

**53162-0015 261206 Gilmore, R. G. and S. K. Bommegowda, “An acute oral neurotoxicity screening study with technical grade Flumethrin in Wistar rats,” Bayer CropScience LP, Stilwell, KS, 5/20/08. Laboratory Study # 07-N12-KK. Groups of 12 rats/sex were administered Flumethrin, 96.0% purity, Batch No. KP03HHE04, by gavage in 5 ml/kg corn oil as a single 0, 1, 5, or 15 mg/kg dose. Due to apparent motor/locomotor activity response in males at 1 mg/kg, a follow-up study was administered in males only with 12 males administered 0, 0.25, or 0.5 mg/kg flumethrin. The latter rats were terminated shortly after day 1 FOB and motor activity measurements. NOEL = 0.5 mg/kg (males) based on reduced motor and locomotor activities (not statistically significant at 1 mg/kg, but plausibly treatment-related).

**53162-0020 261211 Gilmore, R. G. and H. E. Hoss, “A subchronic oral neurotoxicity screening study with technical grade Flumethrin in Wistar rats,” Bayer CropScience LP, Stilwell, KS, 2/21/08. Laboratory Study # 06-N12-GV. Groups of 12 rats/sex were administered Flumethrin [95.8% purity, Batch No. KP03HHE04] by gavage in 5 ml/kg corn oil for 13 weeks at 0, 1, 2.5, or 5 mg/kg/day in a guideline neurotoxicity study. Originally the highest dose was 10 mg/kg/day, however this group showed excessive toxicity including one mortality during the first 3 treatment days. For this reason, surviving 10 mg/kg/day rats were administered 2.5 mg/kg/day thereafter, becoming the mid-dose group. NOEL = 1 mg/kg/day, based on occasional yellow urine staining and red oral stain (both sexes), and on modest body weight decrement associated with modest food consumption decrement (males). Body weights in 5 mg/kg/day males were 23% lower than controls at termination, with associated food consumption decrements. Two males and one female at 5 mg/kg/day were euthanized due to poor condition, typically presenting self-inflicted injuries attributed to paresthesias commonly observed in rats with this class of compounds. Motor activity and locomotor activity was non-significantly reduced in 5 mg/kg/day males and females and marginally so in 2.5 mg/kg/day males; these were plausibly treatment-related. Acceptable. No adverse effects. Major findings were sustained “acute” effects expected with the chemical class: neurohistopathology was negative, and FOB and motor activity responses did not worsen over time. Aldous, Feb. 9, 2012.
**53162-0046  261238  Klein, O., “[Cl-phenyl-U-\(^{14}\)C] Flumethrin: Investigation of the biokinetic behavior and the metabolism in the rat,” Bayer AG, Leverkusen, Germany, 12/21/95, Bayer Study ID 15839. This study used Cl-phenyl-ring labeled flumethrin, administered iv to one lactating cow and one steer. Sacrifice was 8 hrs after dosing. Tissue concentrations were liver >> kidney > muscle or fat (or milk for the cow). Metabolism was highest in the steer. Bayticol acid is the hydrolysis product of flumethrin, with loss of the diphenyl group. In liver of the cow, percent recovered equivalents
of flumethrin, Bayticol acid, and the glucuronide of Bayticol acid were 87%, 7%, and 1%, respectively. Corresponding equivalents for the steer were 29%, 40%, and 7%. In kidney, respective equivalents in the cow were 35%, 47%, and 6%, and in the steer were 16%, 47%, and 25%. Only parent flumethrin was characterized in milk, although an unknown fraction was found comprising 12% of isolated residues. No Bayticol acid nor its glucuronide were found in milk. Muscle and fat had more Bayticol acid than parent flumethrin in both animals. Useful supplementary data, considering that flumethrin is used extensively for domestic animals. No Medical Toxicology Branch worksheet, as farm animal studies are assigned to another unit for review. Aldous, 4/10/12.

53162-0047 261239 Speirs, G. C. and P. Donachie, “The absorption, distribution and elimination of total radioactivity following topical and intravenous administration of [14C]-flumethrin” Inveresk Research, Tranent, Scotland, Bayer Study ID 22818. In Phase 1, 3.3 mg/kg of flumethrin formulated to simulate a topical veterinary product was applied to skin of 2 male sheep for 1 hr, followed by washing. Sacrifice at 24 and 72 hrs found increases in tissue levels over time, with similar concentrations in fat, liver, and kidneys. Somewhat lower concentrations were found in plasma, and lowest in muscle. Phase II was an iv study using 2 sheep per sex at target dose of 1 mg/kg. One per sex was sacrificed at 24 and 72 hrs (but values of the 24-hr male were not usable for technical reasons). By this route, concentrations were liver > plasma or kidneys > fat >> muscle at 24 hrs. Tissue concentrations were typically reduced up to 4-fold by 72 hrs, except that concentrations in fat remained constant. Excretion of Phase I (dermal) over 72 hrs found 1.6% of administered dose in feces, 0.4% in urine, plus 1.0% in cage wash. Dosed skin accounted for 16% of dose, soap wash for 40% of dose, and 21% was retained in the occlusive wrapping materials. At 72 hrs after dosing iv, a cumulative 30% of label was recovered in urine, compared to 44% in feces. Useful supplementary data, considering that flumethrin is used extensively for domestic animals. No Medical Toxicology Branch worksheet, as farm animal studies are assigned to another unit for review. Aldous, 4/10/12.

53162-0048 261240 Phillips, M., “[14C]-Flumethrin: investigation of the nature of metabolites in urine and edible tissues of sheep following intravenous administration” Inveresk Research, Tranent, Scotland, Bayer Study ID 22819. This study reported composition of metabolites in liver and composite fat of the three sheep with usable data as reported in Phase II of Document No. 53162-0047, Record No. 261239, above. In liver, about 40-80% of label was extractable, with Bayticol acid as the dominant material (about 30-60% of total residues), and parent flumethrin as the only other identified material (about 10% of total residues). In fat, about 60-70% of label was extractable, with parent flumethrin accounting for about 40-60% of total residues, compared to 0-3% Bayticol acid. Unknown extractable label constituted 9-20% of residues in fat, compared to 2-6% in liver. Useful supplementary data, considering that flumethrin is used extensively for domestic animals. No Medical Toxicology Branch worksheet, as farm animal studies are assigned to another unit for review. Aldous, 4/11/12.

53162-0049 261241 Gifford, L. J. and J. P. Dunshire, “The metabolism of [14C]-Bayticol in the dairy cow and male beef cattle (live phase),” Inveresk Research International, Tranent, Scotland, 9/16/94, Bayer Study ID 15987. This is the in-life report of study 53162-0046 261238, above. Investigators reported that 4% and 8% of administered iv dose was excreted in urine of the single cow and single steer evaluated, respectively. Tissues were sent to Bayer in Germany, as reported in Record No. 261238, above. Feces and g.i. contents were not evaluated in this short-duration study, and only a liver, kidney, muscle, fat, and milk were examined, as
reported above. Useful supplementary data, considering that flumethrin is used extensively for domestic animals. No Medical Toxicology Branch worksheet, as farm animal studies are assigned to another unit for review. Aldous, 4/11/12.

**SUBCHRONIC (and subacute, if applicable): All species, all routes**

(NOTE: There is no subchronic dog study as of 5/21/2012)

**53162-0022 261213 Bomann, W. and E. Sander, “Investigations of subchronic toxicity in Wistar rats (feeding study over 15 weeks),” Bayer AG, Wuppertal, Germany, April 11, 1995. Bayer ID # 15285. Groups of 20 Wistar [Hsd Win:WU] rats/sex/group were dosed in diet with Bayticol P (Flumethrin), purity 94.6%, Batch 898 230 001 for 15 weeks in a subchronic study at 0, 10, 40, and 160 ppm. Achieved dose levels were 0.7, 2.9, and 11.9 mg/kg/day in treated males and 0.8, 3.4, and 13 in females. NOEL = 10 ppm, based on scratching behavior and associated skin wounds in both sexes at 40 ppm. There was a slight reduction in serum bilirubin at 40 to 160 ppm. In addition to skin lesions and their sequelae, “spastic gait” was a common feature at 160 ppm in both sexes. Acceptable with minor deficiencies. Excessive scratching behavior and associated skin lesions at 160 ppm in this study indicate that the highest dose in subsequent long-term studies should be considerably less than 160 ppm. Aldous, August 7, 2012.

53162-0044 261236 Andrews, P., “Bayticol P and Bayticol P Granulate (c.n. Flumethrin): Study for subchronic oral toxicity in rats (13-week feeding study for pharmacokinetic investigations),” Bayer AG, Wuppertal, Germany, 3/20/2000. Bayer Report 22813. This report compared the responses of a 51.4% formulation (Bayticol P Granulate) and technical flumethrin (93.1% purity) on the basis of a.i. administered. Doses were 50 and 160 ppm (based on a.i.) for each of the above two materials, plus a common control, tested in 10 Wistar rats/sex/group. Body weights were reduced, dose-related, in males for both formulations. Plasma levels of flumethrin (tested only in 160 ppm females) were comparable with both formulations. Clinical signs of “wounds” were dose-related in both sexes with both formulations. Several mortalities occurred at comparable frequencies in both sexes with both formulations at 160 ppm, at about 3 weeks from termination. These results attest to the equivalence of the two formulations (based on a.i. content). Assessed parameters were limited, so this is a supplementary study by design. Results find no changes in NOEL’s nor qualitative differences from other studies (the definitive rat subchronic dietary study is 53162-0022 261213, above). Aldous, no worksheet, 4/4/12.

**53162-0016 261207 Schladt, L., “Flumethrin: Subchronic toxicity study in Wistar rats (13 weeks dermal administration),” Bayer HealthCare AG, Wuppertal, Germany, 8/28/08. Bayer Report No. AD-D-ID# 32570. Ten Wistar rats/sex/group were dosed dermally with Flumethrin, 96% purity, Batch No. KP03HHE04 at 0, 10, 30, or 80 mg/kg/day (week days) in a subchronic study (93 days overall duration, with 6-hr exposures on weekdays: total of 67-68 treatment days). Systemic NOEL = 10 mg/kg/day, based on dose-related body weight decrements in both sexes (statistically significant except in 30 mg/kg/day females), and on “stilted gait” in 2 mid-dose females. Body weight decrements at termination were 10% and 18% for mid-dose and high dose males, and 6% and 10% for corresponding females. There were no definitive or sustained effects at the test site. Incoordinated gait and reduced motility were observed in most 80 mg/kg/day males and females. A high-stepping gait was observed in 9 females and 3 males at 80 mg/kg/day. Thymus weights were significantly reduced at that dose. Thymic atrophy was present or increased in grade at 80 mg/kg/day in both sexes. Increased numbers of 80 mg/kg/day
females had ovarian cysts. Dermal NOEL (M/F) = 80 mg/kg/day (no treatment-related dermal effects at HDT). Acceptable, with no adverse effects. Aldous, August 6, 2012.

53162-0017  261208  Schladt, L., “Flumethrin: Pilot toxicity study in Wistar rats (4 weeks dermal administration),” Bayer HealthCare AG, Wuppertal, Germany, April 2, 2007. Bayer Report No. 30932. Three Wistar rats/sex/group were dosed dermally with Flumethrin, 96% purity, Batch No. KP03HHE04 at 0, 100, 150, or 200 mg/kg/day for 4 weeks. Rats were dosed all week days, plus weekend days in the 4th week, in a subacute pilot study (range-finder for the subchronic dermal study, see DPR Record No. 261207). NOEL < 100 mg/kg/day. All treated groups showed body weight decrements. Clinical signs were observed in all treated groups, most commonly incoordinated gait, reduced motility, increased salivation, bloody muzzle, high-stepping gait, and labored breathing. Necropsy was negative except for wounds in two females, plausibly due to scratching irritated skin. Useful supplementary data, with no adverse effects. Aldous, 3/29/12.

53162-0018  261209  Schladt, L., “Flumethrin active substance: Pilot toxicity study in Wistar rats (2 weeks dermal administration),” Bayer HealthCare AG, Wuppertal, Germany, April 2, 2007. Bayer Report No. 30931. Three Wistar female rats/group were dosed dermally with Flumethrin, 95% purity, at 0, 10, 30, and 100 mg/kg/day for 2 weeks. Rats were dosed all weekdays, plus weekend days in the 2nd week, in a subacute pilot study (range-finder for the subacute dermal study, see DPR Record No. 261208). An additional group of 3 females was dosed with 100 mg/kg/day for 6 days. Apparent NOEL = 10 mg/kg/day (transient body weight decrement at 30 mg/kg/day: decrement more pronounced and longer lasting at 100 mg/kg/day). Clinical signs were limited to 100 mg/kg/day, most commonly incoordinated gait, reduced motility, increased salivation, bloody muzzle, high-stepping gait, and labored breathing. Necropsy was negative. Useful supplementary data, with no adverse effects. No DPR worksheet Aldous, 3/29/12.

53162-0019  261210  Pauluhn, J., “Baytocol P (Flumethrin): Subacute inhalation toxicity on rats (exposure 5 x 6 hr/week for 4 weeks,” Bayer AG, Wuppertal, Germany, 11/13/97. Report ID # 18177. Groups of 10 Wistar rats/sex/group were exposed as above in a study which included a respiratory function segment. Dose levels were 0 (air), 0 [polyethylene glycol 400/ethanol (1:1) carrier], 0.12, 1.33, and 22.4 mg/m³ (average achieved). MMAD was about 1.1 µm, with GSD’s of about 2.0 in treated groups, so that most test article was respirable. NOEL = 0.12 mg/m³, based mainly on clinical signs such as piloerection and ungroomed hair, which persisted at least until the morning after daily treatments on some occasions; also on decreased rectal temperature when assessed shortly after daily treatments, (about 2 °C in both sexes at 1.33 mg/m³, and about 4-6 °C in at 22.36 mg/m³). Clinical signs at 22.4 mg/m³ (when observed prior to the daily administration) additionally included (in high dose females) occasional atony and bradypnea. Observations shortly after daily administration at 22.36 mg/m³ also included salivation and dyspnea. Characteristic clinical signs observed before daily dosing peaked in incidence at about 4-5 days after onset of the treatment regimen: signs observed shortly after treatment were observed throughout the study, and were more frequent than observations before daily exposures. High dose males weighed 12% less than controls at termination. Spleen and thymus absolute and relative weights decreased in high dose males and females. Lung function tests were performed in 8 males/group during a single exposure period during week 3. High dose males showed marked reductions in minute volume and respiratory rate. Peak flow rates for inspiration and expiration were reduced, and expiratory time was increased at this dose. Four high dose males were implanted with EKG electrodes and evaluated pre-study, then at weekly...
Intervals thereafter (shortly after daily treatments): no specific alterations were observed. The latter 4 high dose males were also tested for several respiratory parameters such as O$_2$ consumption, CO$_2$ production, and heat generation. Assessments were done pre-treatment, weekly (recording just after a day’s 6-hr exposure), and once during the week after the exposure period. Primary apparent effects were observed during the first few hours of recording after the end of the first 6-hr exposure. For example, “RER” or the ratio of VCO$_2$/VO$_2$ appears was greatly reduced during the first few hours after the first 6-hr exposure, with subsequent recordings comparable with pre-exposure values. Similarly, reduced heat production and reduced respiratory rate (breaths per minute) were only observed after the first 6-hr period. Histopathology, with particular attention to respiratory tissues, found no effects. Investigators consider the overall respiratory function data to support an “upper respiratory tract sensory irritant,” based on above observations of respiratory parameters. Valid supplementary study, with no adverse effects. Aldous, 2/21/12.

**IMMUNOTOXICITY**

**53162-0050  261242  Schladt, L. and H. W. Vohr, “Flumethrin: Subacute oral immunotoxicity study in Wistar rats (4 weeks administration by diet),” Bayer Schering Pharma AG, Wuppertal, Germany,  9/29/09, Bayer Report No. 35217.** Groups of 8 Wistar rats /sex/group were dosed in diet for 29-30 days with Bayticol P (Flumethrin), Batch No. KP03HHE04, purity 96.0 %. Doses were 0, 10, 40, and 160 ppm, corresponding to 0.8, 3.0, and 11.7 mg/kg/day for males, and 1.0, 3.5, and 12.3 mg/kg/day for females. Isolated spleen cells were counted. Flow cytometric analyses of spleen cells were performed using antibodies to assay major cell types based on surface markers. ELISA techniques were used to assay IgG, IgM, and IgA titers in blood. The “plaque forming cell assay” (PFC) was undertaken by treating rats iv with sheep RBC’s 5 days before sacrifice. Spleen cells were isolated to assess plaque-forming cells in the presence of Guinea pig complement. Clinical effects were limited to bloody muzzle and high-stepping gait, each observed in the same female at 160 ppm. Body weights of 160 ppm rats were significantly (p < 0.01) reduced in both sexes by day 4, with minor decrements remaining until sacrifice. Spleen cell counts were not affected by treatment. There were no changes in the cell types assessed from spleen cells in flow cytometry. Antibody titers in sera were unaffected, however IgG titers were highly variable, thus not very informative. PFC evaluations were uneventful for males. High dose females had about a 50% increase in PFC’s compared to other groups. Individual values varied substantially. Investigators judged that the elevation in females may have been treatment-related, but likely associated with the parasthesias: in any case, this assay was not very sensitive. Organ weights (spleen and thymus) were unaffected by treatment. Study is acceptable, with no adverse effects. Although some parameters were so variable that modest change could not be detected, sample sizes met guidelines and study conduct indicated a valid study. Aldous, April 3, 2012.

**COMPANION ANIMAL SAFETY**

NOTE: DPR reviewer (Aldous) considered the puppy and kitten collar studies acceptable, but did not accept the adult dog and cat studies, because the multiple collar tests evidently greatly under-estimated the exposures. These studies plus a “Miscellaneous” report below [53162-0091 261364 Lunchick, C., “Occupational and residential exposure and risk assessment for PNR 1427
dog and cat collars formulated with imidacloprid and flumethrin,” (not an individual study report), 8/26/10. Bayer Report No. 33861] indicate that one should not expect transfer of flumethrin to animal fur to be proportional to the numbers of collars worn (in 3-collar and 5-collar tests), due to evident slow transfer of flumethrin from core of collar to exterior of collar, and to possible saturation kinetics for transfer from collars to fur or skin. Aldous, 5/21/12.

53162-0060 261261 Madsen, T. J., “Safety of PNR1427 in adult cats,” Sinclair Research Center, LLC, Auxvasse, MO, April 1, 2010, Bayer Report # 33800. Groups of 3 domestic cats/sex were dosed by plastic collars. Treated collars contained about 10.2% imidacloprid and 4.5% flumethrin by weight. Groups were untreated controls, collar-only (no pesticide) controls carrying 5 untreated collars, single collar treatment (a given collar worn for 61 days), and 5-x treatment group (5 treated collars at a time, exchanged for a fresh set at days 0, 14, 28, and 42). Samples of collars were removed following use and assayed for the two pesticides. Imidacloprid and flumethrin exposures were estimated to have been 99 mg/kg/day and 19 mg/kg/cat, respectively for the single treated collar group for the 61-day period. Estimated exposures to 5-collar cats averaged 135, 134, 209, and 184 mg/kg for imidacloprid during periods 0-14 days, 14-28 days, 28-42 days, and 42-61 days. Corresponding exposures to flumethrin in the 5-collar cats were 0, 0, 12, and 13 mg/kg for the respective time periods (the zero values being improbable, resulting from average remaining flumethrin at the end of each 14-day period being about the same as the average collar content of fresh collars). Assessed parameters (body weight, food consumption, hematology, clinical chemistry, clinical signs) did not indicate treatment effects. Supplementary data of limited usefulness due to lack of plausible exposure estimates for flumethrin. Aldous, 5/15/12.

53162-0059 261260 This report is a 2-page table of calculations of imidacloprid and flumethrin release from collars per individual cat. Data do not change study status. Aldous, 5/18/12 (no worksheet).

**53162-0063 261264 Madsen, T. J., “Safety of PNR1427 in kittens,” Sinclair Research Center, LLC, Auxvasse, MO, 6/16/10. Bayer Report # 33824. Groups of 3 to 6 domestic kittens/sex were dosed by plastic collars for 180 days. Treated collars contained 9.9% to 10.2% imidacloprid and 4.5% to 4.7% flumethrin by weight. Groups were untreated controls, collar-only (no pesticide) controls carrying 5 untreated collars, single collar treatment (fresh collars on days 0, 29, 90, and 148), and 3-x and 5-x treatment groups (5 treated collars at a time, Day 0 collars exchanged for fresh sets at days 29, 90, and 148). Samples of collars were removed following use and assayed for the two pesticides. Imidacloprid exposures were estimated to have been 369, 1326, and 1156 mg/kg for kittens wearing 1, 3, and 5 collars, respectively. Flumethrin exposures were estimated to have been 31, 159, and 173 mg/kg for respective groups. Assessed parameters (body weight, food consumption, hematology, clinical chemistry, clinical signs) did not indicate treatment effects. Acceptable, with no adverse effects. Aldous, 5/15/12.

53162-0061 261262 Madsen, T. J., “Safety of PNR1427 in adult dogs,” Bayer HealthCare LLC, Shawnee Mission, KS, 4/23/10. Bayer Report # 33805. Groups of at least 3 beagle dogs/sex were dosed by plastic collars. Treated collars contained about 10% imidacloprid and 4.5% flumethrin by weight. Groups were untreated controls, collar-only (no pesticide) controls carrying 5 collars without active ingredients, single collar treatment (a given collar worn for 61 days), and 5-x treatment group (5 treated collars at a time, exchanged for a fresh set at days 0, 14, 28, and 42). [N = 6/sex in the latter group only.] Samples of collars were removed following...
use and assayed for the two pesticides. Imidacloprid and flumethrin exposures were estimated to have been 83 mg/kg/day and 9.1 mg/kg/dog, respectively for the single treated collar group for the 61-day period. Estimated exposures to 5-collar dogs averaged 192, 225, 237, and 253 mg/kg for imidacloprid during days 0-14, 14-28, 28-42, and 42-61. Corresponding exposures to flumethrin in the 5-collar cats were 0, 0, 0, and 0 mg/kg for the respective time periods (the zero values being improbable, resulting from average remaining flumethrin at the end of each period being slightly less than the average collar content of fresh collars). Assessed parameters (body weight, food consumption, hematology, clinical chemistry, and clinical signs) did not indicate treatment effects. Supplementary data of limited usefulness because no flumethrin decline could be detected in 5-collar dogs. Aldous, 5/16/12.

**53162-0062  261263  Madsen, T. J., “Safety of PNR1427 in puppies,” Bayer HealthCare LLC, Shawnee Mission, KS, 6/16/10.  Bayer Report # 33806.  Groups of six beagle puppies/sex were dosed by plastic collars (3/sex for untreated and placebo collar groups) for 180 days. Treated collars contained about 10% imidacloprid and 4.5% flumethrin by weight. Groups were untreated controls, collar-only (no pesticide) controls carrying 5 untreated collars, single treated collar (fresh collars on days 0, 29, 90, 125, and 148), and 3-x and 5-x treatment groups (3 or 5 treated collars at a time, Day 0 collars exchanged for fresh sets at days , 29, 90, 125, and 148). Samples of collars were removed after use and assayed for the two pesticides. Total imidacloprid exposures were estimated to have been 329 mg/kg for the 1x group, 992 mg/kg for the 3x group, and 1607 mg/kg for the 5x group. Flumethrin exposures were estimated to have been 59 mg/kg for the 1x group, 144 mg/kg for the 3x group, and 85 mg/kg for the 5x group. Assessed parameters (body weight, food consumption, hematology, clinical chemistry, clinical signs) did not indicate treatment effects. Estimated achieved flumethrin doses for the 3-collar and 5-collar groups were about 2.4-fold and 1.4-fold higher than for the 1-collar group for flumethrin, respectively. In contrast, the other active ingredient, imidacloprid, was apparently released in proportion to the numbers of collars. Thus it appears from imidacloprid losses that puppies were properly exposed to the collars, but that flumethrin transfer to the fur may be limited at high doses, as though the fur had become sufficiently saturated as to cause slow transfer from the collar bundles, approaching “zero order” kinetics. Acceptable. There were no adverse effects. Aldous, 5/18/12.

DEVELOPMENTAL NEUROTOXICITY, RAT

**53162-0032  261224  Sheets, L. P., R. G. Gilmore, and H. E. Hoss, “A developmental neurotoxicity study with technical grade flumethrin in Wistar rats,” Bayer CropScience LP, Stilwell, KS, 5/30/08.  Bayer Report # 201747.  Thirty mated females were dosed with 0, 0.5, 1.0, or 2.0 mg/kg/day of Technical flumethrin, Batch KP03HHE04, purity (sum of trans-Z-isomers) = 95.8% in a complete developmental neurotoxicity study. Twenty-one to 23 litters which met criteria were retained to evaluate the typical components of this study type. Maternal NOEL = 1 mg/kg/day, based on decreased food consumption during gestation days 13-20, and attendant decreased gestation maternal body weight gain. Developmental NOEL = 1 mg/kg/day, based on marginally significant decrements in pup body weights. Study is acceptable, with no adverse effects. Aldous, 12/22/11.
MISCELLANEOUS STUDIES

53162-0091  261364  Lunchick, C., “Occupational and residential exposure and risk assessment for PNR 1427 dog and cat collars formulated with imidacloprid and flumethrin,” (not an individual study report), 8/26/10. Bayer Report No. 33861. Many studies using collars containing about 10% imidacloprid and about 4.5% flumethrin in dogs and cats revealed that about 40% of imidacloprid was released over about 8 months, compared to about 20% of flumethrin in the same period. These figures apply to the small collars designed for cats and smaller dog breeds, as well as for the larger collars for dogs > 8 kg. Hair coat content of flumethrin was relatively steady over the entire 8-month period, whereas hair content of imidacloprid after 6-8 months was about one-third of concentration during the first 3 months. Distribution of collar contents of active ingredients to collar surface (assessed by wiping with surface wipes containing solvents) was lower for flumethrin than for imidacloprid at any time assessed: at day 2, surface wipe yields were about 1.7% and 10.5% for flumethrin and imidacloprid, respectively. This is a summary and assessment of many studies, particularly studies involving small numbers of dogs or cats evaluated for a.i. transfers from collars over studies of up to 8 months. Useful supplementary information. Aldous, 5/21/12.

53162-0064  261265, 53162-0065  261266, 53162-0066  261267, and 53162-0067  261268. These were four studies in which collars were applied with or without safety reflectors to puppies, kittens, or adult cats or dogs, respectively. Addition of reflectors did not increase the rate of weight loss of the collars, hence no safety issues arose. There was no apparent need to do chemical assays for the residual active ingredients in these cases. Useful supplementary information. No DPR worksheets. Aldous, 5/21/12.