

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
FLUXAPYROXAD

Chemical Code # 6033, Document Processing Number (DPN) # 53118
SB 950 # (Not applicable)
Original date: Oct 10, 2011
Revised date: (Not applicable)

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect (but see oncogenicity, rat)
Chronic toxicity, dog:	No data gap, possible adverse effect
Oncogenicity, rat:	No data gap, possible adverse effect
Oncogenicity, mouse:	No data gap, no adverse effect
Reproduction, rat:	No data gap, no adverse effect
Developmental toxicity, rat:	No data gap, no adverse effect
Developmental toxicity, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, possible adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

All record numbers for the above study types through 254228 (Document No. 53118-0083) were examined. This includes all relevant studies indexed by DPR as of 8/29/11.

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: t20111010.wpd

Revised by: C. Aldous, 10/10/11(original)

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II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

COMBINED, RAT

****53118-0051 254137** Buesen, R., V. Strauss, A. Groeters, E. Fabian, and W. Mellert, "BAS 700 F - Combined chronic toxicity/carcinogenicity study in Wistar rats - administration via the diet up to 24 months," BASF, Ludwigshafen, Germany, 10/19/09. Laboratory Study # 2009/1072490. Groups of fifty rats/sex/group were dosed in diet with BAS 700 F [Fluxapyroxad], purity 99.7%, for 2 yrs in an oncogenicity study at 0, 50, 250, 1500, or 3000 ppm. An additional 10/sex/group were dosed at those levels for 12 months as satellite chronic study rats. Estimated mean lifetime study exposures were 2.1, 11, 68, and 145 mg/kg/day for increasing dose groups of males, and 2.7, 14, 82, and 182 mg/kg/day for females. NOEL = 50 ppm [M: 2.1 mg/kg/day, F: 2.7 mg/kg/day], with liver as primary target organ. Centrilobular hypertrophy was elevated in lifetime study at 250-3000 ppm in both sexes, in satellite study males at 1500-3000 ppm and females at 250-3000 ppm. Liver absolute and relative weights were elevated at 250-3000 ppm in satellite study females and in males in the lifetime study, and at 1500-3000 ppm in lifetime study females and satellite study males. The relative liver weights of the 250 ppm lifetime study females were also elevated. The most consistent clinical chemistry change was dose-related increase in cholesterol at 250-3000 ppm in males and at 1500-3000 ppm in females. Various other findings at 250 ppm and above included decreased body weight in females (final yr of study) and a sharply dose-related increase in ferric iron deposition in femur cancellous bone evidenced by Perl's Prussian Blue stain in both sexes. There was a dose-related increase in hepatocellular adenoma in 1500-3000 ppm males and in 3000 ppm females. Hepatocellular carcinoma was elevated significantly in 3000 ppm males. Non-significant increases in hepatocellular adenomas in 250 ppm males and in 1500 ppm females were plausibly also treatment-related. Additional associated hepatotoxicity was manifested by strongly dose-related spongiosis in 1500-3000 males, and by pigment accumulation (probably lipofuscin) in 1500-3000 ppm males and females. A strong hyperostosis response was observed in bones of the skull in 3000 ppm males and females. Thyroid gland follicular cell hyperplasia was observed in 1500-3000 ppm males. Tooth whitening was observed in incisors of many males and females at 1500-3000 ppm, without evident microscopic change. Thyroid follicular cell hyperplasia was elevated in 1500-3000 ppm males. Thyroid follicular cell combined adenoma plus carcinoma incidence was statistically elevated in 3000 ppm males compared to concurrent controls. Overall follicular cell tumor incidence was within historical control range, yet some supplementary studies cited in the present DPR review support the plausibility of a treatment effect on follicular tumors, likely mediated by enhanced liver metabolism of thyroxin. Study is **acceptable**. Hepatocellular tumors are "**possible adverse effects**:" noted to exist along with predisposing pathology. Aldous, 8/31/11.

CHRONIC TOXICITY, RAT

See COMBINED, RAT (above)

CHRONIC TOXICITY, DOG

****53118-0049 254135** Hempel, K., V. Strauss, S. Groeters, E. Fabian, and B. van Ravenzwaay, "BAS 700 F - Chronic toxicity study in beagle dogs - administration in the diet for 12 months," BASF SE, Ludwigshafen, Germany, 10/15/09. Laboratory Study # 2008/1090458, Report No. 33D0683/05088. Groups of 5 beagles/sex/group were dosed in diet with BAS 700 F (fluxapyroxad, Batch COD-001026, purity 99.4%) for 1 year in a chronic study. Dietary levels were 0, 300, 1500, and 12000 ppm for males, and 0, 300, 1500, and 9000 ppm for females. Achieved dose levels for respective male treated groups were 8, 39, and 335 mg/kg/day. Corresponding levels for females were 9, 43, and 257 mg/kg/day. NOEL = 300 ppm, based on dose-related iron staining (Perl's Prussian blue positive) in liver and spleen (both sexes), and fibrosis in liver (females). Livers showed fine granular intra-cytoplasmic staining, most pronounced in the peri-portal areas, largely in subcapsular locations. Splenic pigment concentrated in intra-cytoplasmic areas of connective tissue elements, and was evidently not hemosiderin. Liver-associated clinical chemistry changes included dose-related decreases in circulating albumin with a probable secondary reduction in circulating calcium in males, reduced bilirubin (both sexes), and reduced cholesterol (males). Gallbladders had pigmentation in both sexes at 1500 ppm and above. All of the above findings were evident in both sexes at respective highest dose levels. Other findings at 9000-12000 ppm included marked reduction of food consumption in females and prostate atrophy in males (reduced tissue mass, but normal microscopic appearance). The following were seen in both sexes at 9000-12000 ppm: transitory vomiting (at initiation of study), modest body weight decrements, a general increase in platelet counts, very sharply increased serum alkaline phosphatase and gamma-glutamyltransferase (consistent with hepato-biliary toxicity), and sharply elevated liver weights. Study is acceptable, with liver fibrosis as a "possible adverse effect." Aldous, Oct. 7, 2011.

ONCOGENICITY, RAT

See COMBINED, RAT (above)

ONCOGENICITY, MOUSE

****53118-0050 254136** Buesen, R., K. Kuettler, V. Strauss, and B. van Ravenzwaay, "BAS 700 F - Carcinogenicity study in C57BL/6 J Rj mice - administration via the diet over 18 months" (including Amendment No. 1), BASF SE, Ludwigshafen, Germany, Feb. 4, 2010 (amended). BASF Registration Document No. 2010/7003500. Report No. 87C0683/05082. Groups of 50 mice/sex/group were dosed in diet with 0, 150, 750, 3000, or 6000 ppm fluxapyroxad (Batch COD-001049, purity 99.2%) in the oncogenicity study (18 months). An additional 10/sex were assigned to satellite groups at 0 or 6000 ppm (9 months). Estimated achieved dose levels in treated oncogenicity study males were 21, 107, 468, and 996 mg/kg/day, respectively. Corresponding female dose levels were 33, 158, 652, and 1307 mg/kg/day. NOEL = 150 ppm, based on macrovesicular fatty change in livers of both sexes at 750 ppm and above in oncogenicity study mice. Treatment-related increases in liver weights were observed in males at 750 ppm and above, and in females at 3000 and 6000 ppm. Body weights were reduced in dose-related fashion in 3000 to 6000 ppm males, and transiently also in 6000 ppm females. Incisors,

particularly mandibular, had a whitish discoloration at 3000-6000 ppm in both sexes, with 2 affected females at 750 ppm. Study is acceptable, with no adverse effects. Aldous Oct. 6, 2011.

REPRODUCTION, RAT

**53118-0054 254140 Schneider, S., V. Strauss, S. Groeters, and W. Mellert, "BAS 700 F - Two-generation reproduction toxicity study in Wistar rats - administration via the diet," BASF SE, Ludwigshafen, Germany, 10/21/09. Laboratory Study # 2009/1072491, Report No. 70R0683/05092. Wistar rats, 25/sex/group, were dosed in diet to achieve 0, 10, 50, or 300 mg/kg/day in a standard 2-generation reproduction study. Parental systemic toxicity NOEL < 10 mg/kg/day, based on increased absolute liver weights in F1 adults, and dose-related centrilobular hypertrophy in both sexes of both generations. Parental reproductive effects NOEL = 300 mg/kg/day (highest dose tested). Offspring viability and growth NOEL = 50 mg/kg/day (body weight decrement for pups in both generations). The highest dose level was clearly rigorous, eliciting significant decrements in food consumption and body weight, and additional signs of marked liver toxicity at that dose included gross enlargement and discoloration, hepatocellular necrosis in 5-6 males/generation, and highly elevated serum gamma-glutamyltransferase (SGGT) in both generations of both sexes. Thyroid follicular hypertrophy/hyperplasia and altered colloid were observed at 50-300 mg/kg/day. Acceptable, with no adverse effects. Aldous, Oct. 6, 2011.

DEVELOPMENTAL TOXICITY, RAT

**53118-0052 254138 Buesen, R., V. Strauss, W. Kaufmann, E. Fabian, and B. van Ravenzwaay, "BAS 700 F - Prenatal developmental toxicity study in Wistar rats - oral administration (gavage)," BASF SE, Ludwigshafen, Germany, Oct. 8, 2009. Laboratory Study # 2009/1072492, Project No. 30R0683/05094. Groups of 25 mated female Wistar rats/group were dosed with BAS 700 F (fluxapyroxad, Batch COD-000899, purity 99.7%) daily from gestation days 6-19 at 0, 25, 200, or 1000 mg/kg/day. Maternal NOEL < 25 mg/kg/day, based on modest increases in relative thyroid gland weights. Developmental toxicity NOEL = 1000 mg/kg/day (no effect at highest dose tested). Common dose-related maternal changes at 200 to 1000 mg/kg/day included transiently reduced food consumption during the first 2 days of dosing, with significant body weight gain decrements during that period. Reduced serum bilirubin and increased albumin, each likely related to altered liver function, were observed in the same dose range. Study is acceptable, with no adverse effects. Aldous, Oct. 6, 2011.

DEVELOPMENTAL TOXICITY, RABBIT

**53118-0053 254139 Buesen, R., E. Fabian, and B. van Ravenzwaay, "BAS 700 F - Prenatal developmental toxicity study in Himalayan rabbits - oral administration (gavage)," BASF SE, Ludwigshafen, Germany, Oct. 8, 2009, Laboratory Study # 2009/1072493, Project No. 40R0683/05089. Groups of 25 artificially inseminated rabbits/group were dosed with BAS 700 F (fluxapyroxad, Batch COD-000899, purity 99.7%) daily from gestation days 6-28, at 0, 10, 25, or 60 mg/kg/day. Maternal NOEL = 25 mg/kg/day. Food consumption was sharply reduced in high dose does through about day 22. Body weight gain was reduced in these does between days

9 and 16. Additionally, clinical signs of “reduced defecation” were noted in 8 high dose does. Developmental NOEL = 25 mg/kg/day (paw hyperflexion). Study is acceptable, with no adverse effects. Aldous, Oct. 6, 2011.

GENE MUTATION

**53118-0055 254141 Schulz, M. and R. Landsiedel, “BAS 700 F - *Salmonella typhimurium* / *Escherichia coli* reverse mutation assay (standard plate test and preincubation test),” BASF SE, Ludwigshafen, Germany, 10/13/08, Laboratory Study # 2008/1028479. This standard reverse mutation assay used three replicates/dose with and without S-9 activation. *Salmonella* strains were TA 98, TA 100, TA 1535, and TA 1537. *E. coli* strain was WP2 uvrA. Dose levels for fluxapyroxad [BAS 700 F (Batch COD-001026, purity 99.4%)] were uniformly 0, 20, 100, 500, 2500, and 5000 µg/plate. There were no remarkable increases in revertants. Precipitation was observed in all groups at 500 µg/plate and above. Commonly there were dose-related reductions in the numbers of revertants at 2500 to 5000 µg/plate, indicating cytotoxicity. Titer of viable cells, assessed in 2500 to 5000 µg/plate groups with S-9 activation, was commonly reduced in dose-related fashion in the latter dose range. Positive controls were functional. Study is acceptable, with no adverse effects. Aldous, Oct. 4, 2011.

**53118-0055 254142 Schulz, M. and R. Landsiedel, “BAS 700 F: *Salmonella typhimurium* / *Escherichia coli* reverse mutation assay (standard plate test and preincubation test),” Oct. 6, 2009, Laboratory Study # 2009/1080768. This standard reverse mutation assay used three replicates/dose with and without S-9 activation. Study is analogous to Record No. 254141, but used a different batch [No. 35575/18] of BAS 700 F [Fluxapyroxad], purity 96.7%. *Salmonella* strains were TA 98, TA 100, TA 1535, and TA 1537. *E. coli* strain was WP2 uvrA. Dose levels for fluxapyroxad were normally 0, 21, 106, 2650, and 5300 µg/plate (maximum dose levels were 2650 and 530 µg/plate, respectively, for TA 1537 and TA 98 in preincubation assay only). There were no increases in revertants. Precipitation was observed in all groups at 530 µg/plate and above. Commonly there were dose-related reductions in revertants at 2650 to 5300 µg/plate, indicating cytotoxicity. Titer of viable cells, assessed in the two highest two dose groups with S-9 activation, was commonly reduced in dose-related fashion in the latter dose range, and possibly as low as 265 µg/plate in the preincubation test of TA 98 with activation. Positive controls were functional. Study is acceptable, with no adverse effects. Aldous, Oct. 4, 2011.

**53118-0055 254144 Schulz, M. and R. Landsiedel, “*In vitro* gene mutation test in CHO cells (HPRT locus assay) with Reg. No. 5094351,” BASF AG, Ludwigshafen, Germany, 6/19/07. Laboratory Study # 2007/1020715. Test article was BAS 700 F [Fluxapyroxad], Batch COD-000899, purity 99.7%. There were two experiments, each with and without S-9. Limiting cytotoxicity ranged from 50 to 75 µg/ml. The first experiment used dose levels of 0, 5, 10, 20, 50, and 100 µg/ml fluxapyroxad. The second experiment used 6.3, 12.5, 25, 50, 75, and 100 µg/ml. There were two flasks per dose level. About 1×10^6 cells per flask were initiated on study. Treatment did not elicit mutagenicity. Positive controls (EMS without S-9 and MCA with S-9) were functional. Acceptable. No adverse effects. Aldous, 6/29/11.

**53118-0055 254146 Schulz, M. and R. Landsiedel, “BAS 700 F: *In vitro* gene mutation test in CHO cells (HPRT locus assay),” BASF SE, Ludwigshafen, Germany, Oct. 2, 2009, 2009/1078663. Test article was BAS 700 F [Fluxapyroxad], Batch 35575/18, purity 96.7%.

There were two initial experiments, each with and without S-9. A third experiment with S-9 was undertaken for technical reasons. Limiting cytotoxicity was 75 µg/ml without S-9, and about 120-125 µg/ml with S-9. There were two flasks per dose level. About 1 x 10⁶ cells per flask were initiated on study. Treatment did not elicit mutagenicity. Positive controls (EMS without S-9 and MCA with S-9) were functional. Acceptable: there were sufficient concentrations closely spaced near to optimal levels for a thorough assessment. No adverse effects. Aldous, 6/29/11.

CHROMOSOME EFFECTS

****53118-0056 254156** Schulz, M. and R. Landsiedel, "Cytogenetic study in vivo with LS 5094351 in the mouse micronucleus test after two oral administrations," BASF AG, Ludwigshafen, Germany, Dec. 6, 2006. Laboratory Study # 2006/1032708. Five male Crl:NMRI mice/group were dosed twice orally (10 ml/kg corn oil suspension) with 0, 500, 1000, or 2000 mg/kg LS 5094351 (fluxapyroxad, Batch COD-000826, purity 99.6%) 24 hrs before sacrifice. Positive controls were 20 mg/kg cyclophosphamide and 0.15 mg/kg vincristine sulfate, each with 24-hr intervals. No treatments caused clinical effects. Fluxapyroxad groups had no increases in micronuclei. Positive controls were functional, with cyclophosphamide eliciting numerous small micronuclei, and vincristine causing large numbers of large and small micronuclei. Acceptable, with no adverse effects. Aldous, Oct. 5, 2011.

****53118-0057 254157** Schulz, M. and R. Landsiedel, "BAS 700 F - Micronucleus test in bone marrow cells of the mouse," BASF SE, Ludwigshafen, Germany, Oct. 2, 2009. Laboratory Study # 2009/1072522. Five male Crl:NMRI mice/group were dosed ip (in 4 ml/kg DMSO) with 0, 500, 1000, or 2000 mg/kg BAS 700 F [Fluxapyroxad, Batch 35575/18, purity 96.7%], 24 hrs before sacrifice. An additional 5 males/group received 0 or 2000 mg/kg fluxapyroxad, with a 48-hr interval to sacrifice. Positive controls were 20 mg/kg cyclophosphamide and 0.15 mg/kg vincristine sulfate, each with 24-hr intervals. No treatments caused clinical effects. Fluxapyroxad groups had no increases in micronuclei. Positive controls were functional, with cyclophosphamide eliciting numerous small micronuclei, and vincristine causing large numbers of large and small micronuclei. Acceptable, with no adverse effects. Aldous, Oct. 6, 2011.

****53118-0056 254148** Schulz, M. and R. Landsiedel, "BAS 700 F - *In vitro* chromosomal aberration assay in V79 cells," BASF AG, Ludwigshafen, Germany, 1/22/08. Laboratory Study # 2007/1023153. V79 cell line cultures of about 30000 to 80000 cells per culture were treated with at least 0, 12.5, 25, 50, and 100 µg/ml BAS 700 F [Fluxapyroxad], Batch COD-000899, purity 99.7% in two experiments, with 2 cultures per treatment combination (from which 200 spreads were evaluated per treatment combination). Exposure durations and total time to harvest in the first experiment were 4 hrs/18 hrs with or without S-9. In the second experiment, these times were 18 hrs/18 hrs and 18 hrs/28 hrs without S-9, and 4 hrs/28 hrs with S-9. Colcemid was used to arrest mitosis. In all cases, 50 µg/ml was the maximum dose with sufficient readable spreads for analysis. Fluxapyroxad did not elicit chromosomal aberrations. Mitotic index was unaffected by treatment. Study is acceptable, with no adverse effects. Aldous, 6/30/11.

****53118-0056 254149** Schulz, M. and R. Landsiedel, "BAS 700 F: *In vitro* chromosomal aberration assay in V79 cells," BASF SE, Ludwigshafen, Germany, Oct. 1, 2009. Laboratory

Study # 2009/1078662. V79 cell line cultures of about 30000 to 80000 cells per culture were treated with BAS 700 F [Fluxapyroxad], Batch 35575/18, purity 96.7%, in 3 experiments, with 2 cultures per treatment combination (from which normally 200 spreads were evaluated per treatment combination). Exposure durations and total time to harvest in the first and third experiments were 4 hrs/18 hrs with or without S-9. In the second experiment, these times were 18 hrs/18 hrs and 18 hrs/28 hrs without S-9, and 4 hrs/28 hrs with S-9. Colcemid was used to arrest mitosis. Fluxapyroxad elicited chromosomal aberrations in the entire range of 60 to 80 µg/ml Experiment 3 (significantly elevated compared to concurrent controls, and outside the historical range at all three dose levels, with and without S-9). This range was close to toxicity limits, with cell numbers at 80 µg/ml reduced to 59% of controls without S-9, and to 48% of controls with S-9. Also, in the case of treatment without S-9 in Experiment 3, cell morphology was atypical (“rounded”) and cells had markedly reduced attachment compared to controls at 40-80 µg/ml. In contrast, these treatment levels in groups treated with S-9 in Experiment 3 had normal cell morphology. In Experiment 1, there were small increases in chromosomal aberrations at the maximum readable dose of 62.5 µg/ml, with and without S-9 (not statistically significant compared to concurrent controls, but outside historical control range for the laboratory). Incidence of polyploidy was unaffected by treatment. Study is acceptable, with a “possible adverse effect” of chromosomal aberrations. Aldous, 6/30/11.

DNA DAMAGE

**53118-0057 254158 Schulz, M. and R. Landsiedel, “BAS 700 F - In vivo unscheduled DNA synthesis (UDS) assay in rat hepatocytes,” BASF AG, Ludwigshafen, Germany, Nov. 8, 2008 (amended). Laboratory Study # 2008/7020135. Groups of 3 male Wistar rats/group were dosed by oral gavage with 0, 1000, or 2000 mg/kg BAS 700 F [Fluxapyroxad], Batch COD-000899, purity 99.7%, or with 50 mg/kg 2-acetylaminofluorene (positive control) with sampling times of 3 hrs or 14 hrs to sacrifice. Isolated hepatocytes were allowed to attach to wells, treated with ³H-thymidine for 4 hrs, then washed and incubated without radiolabel for another 12 hrs. Cells were processed with photographic emulsions in darkness to visualize ³H disintegration tracks, and stained with H&E. Coded slides were examined for net (nuclear minus cytoplasmic) grain count, with proliferating cells censored. All 2000 mg/kg fluxapyroxad rats showed clinical signs at sacrifice (apathy). Fluxapyroxad did not elicit UDS, whereas positive controls were functional. Study is acceptable, with no adverse effects. Aldous, Oct. 6, 2011.

**53118-0057 254159 Schulz, M. and R. Landsiedel, “BAS 700 F: In vivo unscheduled DNA synthesis (UDS) assay in rat hepatocytes,” BASF AG, Ludwigshafen, Germany, Oct. 1, 2009. Laboratory Study # 2009/1078661. Groups of 3 male Wistar rats/group were dosed *iv* with 0, 2.5 or 5.0 mg/kg BAS 700 F [Fluxapyroxad], Batch 35575/18, purity 96.7%, or by gavage with 50 mg/kg 2-acetylaminofluorene (positive control) with sampling times of 3 hrs or 14 hrs to sacrifice. Isolated hepatocytes were allowed to attach to wells, treated with ³H-thymidine for 4 hrs, then washed and incubated without radiolabel for another 12 hrs. Cells were processed with photographic emulsions in darkness to visualize ³H disintegration tracks, and stained with H&E. Coded slides were examined for net (nuclear minus cytoplasmic) grain count, with proliferating cells censored. There was a dose-response for clinical signs in 2.5 to 5.0 mg/kg fluxapyroxad rats. Piloerection was observed at sacrifice of all fluxapyroxad rats. Fluxapyroxad did not elicit UDS, whereas positive controls were functional. Study is acceptable, with no adverse effects. Aldous, Oct. 6, 2011.

NEUROTOXICITY

53118-0040 254126 Kaspers, U., W. Kaufmann, E. Fabian, and B. van Ravenzwaay, "BAS 700 F - Acute oral neurotoxicity study in Wistar rats - administration via gavage," BASF SE, Ludwigshafen, Germany, Oct. 7, 2009. Laboratory Study # 2009/1065774, Project No. 61S0683/05102. Groups of 10/sex/group were dosed once by gavage (in 1% CMC, 10 ml/kg) at 0, 125, 500, or 2000 mg/kg. FOB and motor activity were assessed pre-study (Day -7), Day 0 (after dosing), Day 7, and Day 14 on all rats. Five/sex were examined in controls and at 2000 mg/kg at termination for neurohistopathology. NOEL = 125 mg/kg, with diminished motor activity at Day 0 as the major finding in both sexes at 500 to 2000 mg/kg. Other findings, both at Day 0, were significantly decreased rearing behavior in 500 to 2000 mg/kg males, and increased landing foot splay in 2000 mg/kg males. Study is not acceptable, but upgradeable: validation of laboratory technicians' ability to identify neurotoxic endpoints is requested. This usually entails positive control validation studies: such studies referenced in the present report were not current, but rather were completed about 7 years or more before this study was undertaken. Aldous, Oct. 7, 2011.

53118-0048 254134 Kaspers, U., V. Strauss, W. Kaufmann, E. Fabian, and W. Mellert, "BAS 700 F - Repeated dose 90-day oral neurotoxicity study in Wistar rats; administration in the diet," BASF SE, Ludwigshafen, Germany, Nov. 2, 2009 (amended), Laboratory Study # 2009/7006263, Project No. 63S0683/05090. Groups of 10 Wistar [CrI:WI(Han)] rats/sex/group were dosed in diet with BAS 700 F (fluxapyroxad, Batch COD-001026, purity 99.4%) at 0, 200, 1000, or 5000 ppm for 3 months. Mean achieved dose levels were 11.5, 58, and 302 mg/kg/day for males, and 13.4, 67, and 338 mg/kg/day for females. Apparent NOEL for neurotoxicity = 5000 ppm (highest dose tested). NOEL for general toxicity < 200 ppm, due primarily to liver and thyroid changes. Hepatocellular hypertrophy was observed in all treated males and in all females from 1000 to 5000 ppm: in each case there was a clear dose-response in degree of hypertrophy. Thyroid weights were progressively elevated in all treatment groups of both sexes. Study protocol did not require microscopic examination of thyroid glands. Major clinical chemistry changes, plausibly related to liver toxicity or to altered liver function, included elevated globulins (all treated male groups, and 1000-5000 ppm females) and significantly elevated albumin at 5000 ppm in both sexes. Serum inorganic phosphorus and calcium were elevated at 5000 ppm in both sexes (possibly reflecting elevated serum carrier proteins). Glucose was sharply reduced in 5000 ppm males. Triglycerides were markedly increased at 5000 ppm, particularly in females. Serum GGT was increased at 5000 ppm in both sexes: profoundly so in males. Study is not acceptable, but upgradeable: validation of laboratory technicians' ability to identify neurotoxic endpoints is requested. This is usually done by positive control validation studies. Such studies referenced in the present report were not current: they were completed about 7 years or more before this study was undertaken. No adverse effects. Aldous, Oct. 7, 2011.

METABOLISM

The following two studies fulfill the biokinetics/metabolic disposition data requirements for fluxapyroxad.

53118-0057 254160 Fabian, E. and R. Landsiedel, "14C-BAS 700 F: Study on the biokinetics in rats," BASF SE, Ludwigshafen, Germany, 9/30/09. Laboratory Study # 2009/1074879. Parent is 3-(difluoromethyl)-1-methyl-N-(3',4',5'-trifluoro[1,1'-biphenyl]-2-yl)1H-pyrazole-4-carboxamide. Unlabeled fluxapyroxad was Batch No. COD-000842, 99.2% purity. Pyrazole-4-¹⁴C label (Batch No. 900-1101, radiochemical purity 99.8%, estimated chemical purity is 99%) was used for blood and plasma kinetics at 5, 50, and 500 mg/kg. Aniline-U-¹⁴C label, Batch No. 916-1018, radiochemical purity 98.2%, chemical purity 97.3%, was used at 7.5 and 150 mg/kg for balance and excretion studies, tissue distribution, and biliary studies. Examination of exhaled air for ¹⁴C-CO₂ residues found negligible label. Record No. 254161 found minimal cleavage between pyrazole and aniline label positions, so that the label placement was arbitrary: aniline label was usually used for the present study. Usually 4 Wistar rats/sex were used at each study phase, dose, and time point combination. At 7.5 mg/kg, about 85-90% of administered dose was found in feces, with 10% and 17% of administered dose in urine of males and females, respectively. Percent of label in urine after 150 mg/kg was reduced in both sexes. About 51-63% of administered dose was excreted via bile in cannulated rats of either sex at 7.5 and 150 mg/kg, thus absorbed dose was about 60-70% of administered dose. Tissue levels after 7 days were low: liver at about 0.1% of administered dose being the most noteworthy. Peak plasma concentrations were delayed as dose increased. T_{max} was 1, 8, and 24 hrs for 5, 50, and 500 mg/kg, regardless of sex. Initial t_{1/2} in plasma ranged from 12-15 hr for 5 mg/kg to 25-27 hrs for 500 mg/kg. Terminal t_{1/2} was > 30 hrs in all cases. Tissue levels in 7.5 mg/kg rats declined normally over time. Highest initial levels (excluding alimentary tract) were adrenal glands, followed in order by liver and thyroid. In females, adipose tissue had higher remaining specific activity than any of these organs at 48 hrs. The 150 mg/kg rats did not indicate remarkable affinity for any tissue, although liver and adipose tissue levels were the highest 16-hr levels. By the time of the final assessment (96 hrs for males and 104 hrs for females), liver had the highest concentration of assessed tissues. Useful segment of the metabolism study series. Aldous, Oct. 6, 2011.

53118-0058 254161 Schopfer, C. and S. Labib, "The metabolism of 14C-BAS 700 F (Reg. No: 5094351) in Wistar rats," BASF SE, Limburgerhof, Germany, 9/24/09. Laboratory Study # 2009/1019789. Samples were primarily taken from the in-life study, 53118-0057 254160 (see Summary of Toxicology Data). Record No. 254160 reported that about 85-90% of administered dose was found in feces. Major metabolites were hydroxylation products of phenyl rings or conjugates thereof. Over one-half of labeled content also had lost the methyl group of the pyrazole. The present study reported disposition of low and high doses of fluxapyroxad (7.5 and 150 mg/kg, respectively). Findings at the 7.5 mg/kg best represent plausible human exposures, and are emphasized in this review. The most abundant fecal metabolite in 7.5 mg/kg males was M700F009 (product of N-demethylation of the pyrazole group, and of hydroxylation of one of the phenyl groups). This was also the dominant metabolite in 7.5 mg/kg females. M700F009 constituted 22% of administered dose in fecal extracts of males, and 53% in females. Metabolite M700F005 (parent with hydroxylation of one of the phenyl groups) constituted 9% of administered dose in feces of males and females. Biliary label accounted for 54-69% of administered dose in cannulated rats, with little influence of sex or dose. The most abundant metabolite in bile of 7.5 mg/kg males (14% of administered dose) was M700F004, a glucuronide of phenyl-hydroxylated parent. M700F004 was also an important biliary metabolite in females (11% of administered dose). Conjugated (glucuronide, cysteine) products of M700F009 and of M700F005 (and of isomers of these two metabolites) were quite common in the bile. The

comparatively large amount of M700F004 in bile compared to feces or urine, plus the more plentiful M700F009 and other conjugated metabolites in feces, gives the impression that intestinal microflora have appreciable glucuronidase activity, as well as possibly N-demethylase activity. Parent fluxapyroxad constituted about 3% of administered dose in feces of either sex. Parent was not found in urine nor bile. In contrast to the above, the most striking feature of high dose treatment was reduced absorption: parent fluxapyroxad constituted 44% of administered dose in males and 34% of administered dose in the feces of the 150 mg/kg males and females, respectively. At the plasma T_{max} for low dose levels (1 hr), liver label concentration was higher than other sampled tissues. In these low dose rats at T_{max} , parent constituted 3.0% and 3.7% of administered dose in the livers of males and females, respectively. Parent comprised 59-70% of label in liver at that time. Useful data in support of metabolism data requirements. Aldous, Oct. 4, 2011.

SUBCHRONIC (and subacute, if applicable)

DOG

**53118-0046 254132 Hempel, K., V. Strauss, A. Gröters, E. Fabian, and B. van Ravenzwaay, "BAS 700 F - Repeated dose 90-day oral toxicity study in beagle dogs - administration in the diet," BASF SE, Ludwigshafen, Germany, 7/16/09. Laboratory Study # 2008/1013661, Report No. 31D0683/05084. Groups of 5 beagles/sex/group were dosed in diet with BAS 700 F (fluxapyroxad, Batch COD-000899, purity 99.7%) for 90 days in a subchronic study. Dietary levels were 0, 300, 1500, and 10000 ppm for males, and 0, 300, 1500, and 7500 ppm for females. Achieved dose levels for respective male treated groups were 9, 45, and 295 mg/kg/day. Corresponding levels for females were 10, 51, and 238 mg/kg/day. NOEL = 300 ppm in both sexes, based on very slight, dose-related reduction of serum albumin. Other possible hepatobiliary responses were elevated alkaline phosphatase and serum γ -glutamyltransferase at 7500 and 10000 ppm. Also at these doses, levels of circulating calcium (which is largely transported on albumin) were measurably reduced. A reduction in total bilirubin at 7500-10000 ppm likely also reflected altered liver function. Liver weights were significantly elevated at these levels, without associated histopathology. Food consumption was reduced in 7500 ppm females. All high dose dogs vomited on the first day, sometimes up to 2 days: an apparent acute effect. Acceptable, with no adverse effects. Aldous, Oct. 7, 2011.

53118-0043 254129 Hempel, K., V. Strauss, A. Gröters, E. Fabian, and B. van Ravenzwaay, "BAS 700 F - Repeated dose 28-day oral toxicity study in beagle dogs - administration in the diet," BASF SE, Ludwigshafen, Germany, July 2, 2009. Laboratory Study # 2007/1052660. Report No. 30D0683/05077. Groups of 5 beagles/sex/group were dosed in diet with BAS 700 F (fluxapyroxad, Batch COD-000899, purity 99.7%) for 34-38 days in a pilot study to assess dose levels for the definitive subchronic study. Dietary levels were 0, 2500, 7500, and 20000 ppm. Achieved dose levels for respective male treated groups were 74, 211, and 521 mg/kg/day. Levels in females were 85, 230, and 503 mg/kg/day. No NOEL was sought nor found. Alkaline phosphatase was elevated in both sexes at all dose levels with marked dose-response. Albumin levels were reduced consistently at all dose levels in both sexes. This study determined that 20000 ppm would be excessive for the primary subchronic study (DPR Record No. 254132): this dose level caused excessive decline in food consumption and greatly diminished uterine and

thymic weights. The dose range selected for the subchronic study was rationally chosen, based on the present "28-day" pilot study. Useful supplementary data. Aldous, Oct. 7, 2011.

RAT

**53118-0044 254130 Kamp, H., V. Strauss, S. Groeters, E. Fabian, and B. van Ravenzwaay, "BAS 700 F - repeated dose 90-day oral toxicity study in Wistar rats; administration in the diet," BASF SE, Ludwigshafen, Germany, Sept. 8, 2009. Laboratory Study # 2007/1005069, Report No. 50C0683/05064. Groups of 10 rats/sex/group were dosed in diet BAS 700 F (fluxapyroxad, Batch COD-000826, purity 99.6%) for 90 days in a subchronic study. Dietary levels were 0, 100, 500, 2000, and 6000 ppm. Achieved dose levels for respective male treated groups were 6.1, 31, 126, and 407 mg/kg/day. Levels for corresponding females were 7.3, 35, 144, and 424 mg/kg/day. NOEL = 100 ppm, based on centrilobular hepatocellular hypertrophy and increased relative liver weights in both sexes. Dose levels of 500-2000 ppm appeared to elicit only adaptive changes. Major findings, typically with clear dose-response, comprising that full range included the above findings in both sexes, plus thyroid follicular cell hypertrophy/hyperplasia in females, and reduced aspartate aminotransferase in males. Hepatic single cell necrosis was observed in 9/10 high dose males, but not in any other groups. This would indicate an excessive dose level for the subsequent chronic study. Thyroid follicular cell hypertrophy and/or hyperplasia was observed at 2000-6000 ppm in males, and at 500-6000 ppm in females, plausibly secondary to liver metabolic induction. Acceptable, with no adverse effects. Aldous, Sept. 2, 2011.

53118-0041 254127 Kamp, H., E. Fabian, V. Strauss, W. Kaufmann, and B. van Ravenzwaay, "BAS 700 F: repeated dose toxicity study in Wistar rats; administration in the diet for 4 weeks," BASF SE, Ludwigshafen, Germany, 10/14/09. Laboratory Study # 2009/7006273. Groups of 5 Wistar rats/sex/group were dosed in diet with Fluxapyroxad (BAS 700 F), Batch 32740/173, purity 99.81%, for 4 weeks in a probe subchronic study. Treatment groups of 0, 100, 500, 2000, and 6000 corresponded to achieved dose levels of 9.0, 44, 176, and 530 mg/kg/day for increasing dose groups of treated males, and of 9.4, 48, 183, and 531 mg/kg/day in females. This was the pilot study for 53118-0044 254130, above. Since this pilot reported comparable effects to the definitive subchronic study, no DPR worksheet is needed. Aldous, 5/10/11.

**53118-0047 25

Kaspers, U., V. Strauss, M. C. Rey Moreno, E. Fabian, and W. Mellert, "BAS 700 F - Repeated dose 28-day dermal toxicity study in Wistar rats," BASF SE, Ludwigshafen, Germany, 10/14/09. Laboratory Study # 2009/1072489. Groups of 10 Wistar rats were dosed on clipped dorsal skin under semi-occlusive dressing for 6 hrs/day, 5 days/week with BAS 700 F (fluxapyroxad), Batch COD-001049, purity 99.2%, at 0, 100, 300, or 1000 mg/kg/day. Suspensions were prepared in 1% aq. CMC at 4 ml/kg b.w. NOEL = 300 mg/kg/day, based on modest liver weight elevation (statistically significant in both sexes at 1000 mg/kg/day). No other effects were identified. Study is acceptable, with no adverse effects. Aldous, Oct. 7, 2011.

MICE

53118-0045 254131 Kamp, H, V. Strauss, A. Groeters, E. Fabian, and B. van Ravenzwaay, "BAS 700 F - Repeated dose 90-day oral toxicity study in C57BL/6 J Rj mice; administration in the diet," BASF SE, Ludwigshafen, Germany, Sept. 11, 2009, Laboratory Study # 2007/1018641. Report No. 51C0683/05070. Groups of ten C57BL/6 J Rj mice/sex/group were dosed in diet BAS 700 F (fluxapyroxad, Batch COD-000826, purity 99.6%) for 92-93 days in a subchronic pilot study at 0, 100, 400, 2000, and 6000 ppm. Mean achieved dose levels were 21, 77, 390, and 1136 mg/kg/day for increasing dose levels in treated males, and 32, 128, 610, and 1657 mg/kg/day in females. NOEL = 100 ppm for males, based on decreased cholesterol and triglycerides, and possibly treatment-related centrilobular fatty change. NOEL for females = 400 ppm, based on decreased albumin and decreased cholesterol. Liver weights were elevated at 2000 and 6000 ppm in both sexes. The highest dose level caused reduced food consumption in both sexes and reduced body weight in males. Study is supplementary by design, undertaken to set dose levels for the mouse oncogenicity study. Aldous, 5/31/11.

53118-0042 254128 Kamp, H, V. Strauss, A. Groeters, E. Fabian, and B. van Ravenzwaay, "BAS 700 F - Repeated dose toxicity study in C57BL/6 J Rj mice; administration in the diet for 4 weeks," BASF SE, Ludwigshafen, Germany, Sept. 11, 2009. Laboratory Study # 2007/1005068. Report No. 31C0683/05067. This was the pilot study which helped set dose levels for the subchronic mouse study, Record No. 254131, above. This pilot study has no bearing on NOEL's or toxicity characterization. No DPR worksheet. Aldous, June 1, 2011.

MECHANISTIC STUDIES RELATING TO COMBINED, RAT

53118-0061 254165 Buesen, R., V. Strauss, E. Fabian, S. Groeters, and B. van Ravenzwaay, "BAS 700 F: Enzyme induction in liver of Wistar rats - administration in the diet over 2 weeks and recovery period of about 4 weeks," BASF SE, Ludwigshafen, Germany, 10/28/09. BASF Registration Document No. 2009/1072495. Ten Wistar rats/sex/group were dosed with fluxapyroxad (99.2% purity) in diet for 2 weeks at 0, 250, 1500, or 3000 ppm. Achieved dose levels in treated males were 16, 96, and 192 mg/kg/day, and in females: 19, 126, and 234 mg/kg/day. Additional groups of 10/sex were similarly dosed for 2 weeks at 0 or 3000 ppm, then taken off treatment for 4 weeks to assess recovery. At term of treatment or recovery, rats were necropsied and examined for histopathology. In addition, liver microsomes were assayed for total cytochrome P-450 content, for activities of primary metabolism: ethoxyresorufin-O-deethylase (EROD), pentoxyresorufin-O-depentylase (PROD), and benzoxyresorufin-O-debenzylase (BROD); and of glucuronosyltransferase activities MUF-GT and HOBI-GT (for 4-methylumbelliferone and 4-hydroxybiphenyl substrates), and the T4-specific UDP-glucuronosyltransferase. Liver weights were significantly elevated in all male groups (107%, 135%, and 152% of control weights in increasing dose groups) and in 1500-3000 ppm females (120% and 144% of controls, respectively). Liver weights were near normal in recovery rats. Thyroid gland weights were significantly elevated in 1500 ppm males (120% of controls), indicating treatment effect. Of thyroid-associated hormones, TSH was significantly elevated in 3000 ppm males only (150% at termination). T3 and T4 levels were unaffected. There were no residual effects on these hormones after recovery. Thyroid follicular hypertrophy/hyperplasia was observed in 250-3000 ppm males and in high dose females. All high dose rats had liver

centrilobular hypertrophy, as also most rats at 1500 ppm rats, and some at 250 ppm. No such histopathology persisted in either organ in recovery rats. Cytochrome P-450 content (ng/mg protein basis) on day 15 was elevated significantly in all groups, to a maximum extent of about 2-fold. EROD activities peaked at about 3-fold over controls. PROD activities were induced up to 20-fold in males and up to 125-fold in females. BROD activities were induced up to 10-fold in males and 127-fold in females. Activity of MUF-GT was increased up to 5-fold in males and 4-fold in females. Similarly, HOBI-GT was elevated up to 5-fold in males and 3-fold in females. T4-UDP-glucuronosyltransferase activity was increased up to a comparatively modest 1.6-fold for males and 2.7-fold for females. The latter is evidently a key factor in rodent thyroid follicular cell cancer induction. In contrast, the primary means of inactivation of T4 in humans is deiodination (A. Parkinson, p. 167, *in* Klaassen, C.D., Ed., Casarett and Doull's Toxicology: The Basic Science of Poisons, Fifth Edition, New York, McGraw-Hill, 1996). Treatment-related increases in the above metabolic enzyme activities were largely or completely reversed in recovery rats. Useful supplementary data. Aldous, Sept. 1, 2011.

53118-0060 254164 Buesen, R., E. Fabian, S. Groeters, and B. van Ravenzwaay, "BAS 700 F: Enzyme induction in liver of Wistar rats - administration in the diet over 2 weeks," BASF SE, Ludwigshafen, Germany, 2/25/10, Laboratory Study # 2009/1072496. Ten Wistar rats/sex/group were dosed with fluxapyroxad (99.2% purity) in diet for 2 weeks at 0 or 50 ppm (3.0 and 3.8 mg/kg/day in males and females, respectively). This is a follow-up of BASF Registration Document # 2009/1072495 (DPR Record No. 254165), which identified liver enzyme induction down to the lowest dose tested (250 ppm). At termination of the present study, rats were necropsied, and liver microsomes were assayed for total cytochrome P-450 content, and for the following liver microsomal activities: ethoxyresorufin-O-deethylase (EROD), pentoxyresorufin-O-depethylase (PROD), and benzoxyresorufin-O-debenzylase (BROD); and of glucuronosyltransferase activities MUF-GT and HOBI-GT (for 4-methylumbelliferone and 4-hydroxybiphenyl substrates), and the T4-specific UDP-glucuronosyltransferase. Treatment caused a statistically significant increase in BROD activity in both sexes (134% of controls in males, and 421% of controls in females). Also significant was increased HOBI-GT activity in males (123% of controls). Useful supplementary information, extending the dose-response relationships to activities below levels of statistical significance in most cases, or to levels which allow extrapolation for well-defined response curves. Aldous, Oct. 6, 2011.

53118-0065 254170 Buesen, R., V. Strauss, E. Fabian, S. Groeters, and B. van Ravenzwaay, "BAS 700 F - Thyroid hormone study: repeated dose oral toxicity study in Wistar rats - administration via the diet for 4 weeks," BASF SE, Ludwigshafen, Germany, 10/20/09. Laboratory Study # 2009/1072497. Ten Wistar rats/sex/group were dosed with fluxapyroxad (99.2% purity) in diet for 4 weeks at 0, 50, 250, 1500, or 3000 ppm. Mean achieved dose levels were 3.5, 19, 105, and 214 mg/kg/day in increasing treated male groups, and 4.4, 20, 117, and 237 mg/kg/day in females. Investigators sampled blood of fasted rats pre-test and on treatment days 3, 7, 14, 21, and 28 to assess thyroid-related hormones: T3, T4, and TSH. Investigators recorded liver and thyroid weights and gross changes, but did not examine tissues microscopically. Absolute NOEL = 50 ppm in males and 250 ppm for females, based on elevated liver weights. NOEL for thyroid-associated hormone levels (parameters of primary interest in this study) = 1500 ppm, based on measurably reduced T4 and elevated TSH in 3000 ppm males only. T3 was unaffected. Liver weights were elevated to 133% and 150% of controls in 1500 ppm and 3000 ppm males, and to 122% and 149% in corresponding females. Aldous, April 1, 2011.

53118-0062 254166 Buesen, R., W. Kaufmann, E. Fabian, and B. van Ravenzwaay, "BAS 700 F - S-phase response study in Wistar rats: administration via the diet for 1, 3, 7 and 14 days," BASF SE, Ludwigshafen, Germany, 2/25/10. Laboratory Study # 2009/1072500. Ten Wistar rats/sex/group were dosed in diet with BAS 700 F [Fluxapyroxad], Batch COD-001049, purity 99.2%, for 1, 3, 7, or 14 days in a supplementary study at 0, 50, 250, 1500, or 3000 ppm. Representative (7-day cohort) achieved dose levels were 3.3, 16, 100, and 183 mg/kg/day for treated males, and 3.5, 17, 92, and 195 mg/kg/day for females. Key parameters examined were liver weights, liver histopathology, and particularly liver cell proliferation (7 days after implanting osmotic pumps delivering BrdU). Liver weights of both sexes were consistently elevated at 1500 and 3000 ppm following treatment of 3 to 14 days. A slight increase in liver weight at day 14 in 250 ppm males was also likely treatment-related. Livers showed dose-related increases in incidence and degree of hepatocellular hypertrophy in males at 250 ppm and above, and in females at 1500 to 3000 ppm. Hypertrophy was observed on days 7-14 in males. Hypertrophy was observed in all 1500-3000 ppm females at day 14, but only in 3000 ppm females during days 3-7. Hepatic cell proliferation was increased after 3-day and 7-day treatments in 1500 and 3000 ppm males and females in all zones. In males the strongest response was in zone 2 (19 to 30-fold), and secondarily in zone 3 (9 to 19-fold) on days 3 and 7. At day 14, the only significant increases in males were in zone 3 (3-fold at 1500 and 3000 ppm). In females, the strongest response was clearly zone 3 (centrilobular). Proliferation was significantly increased in 250 ppm females, primarily in zone 3, at days 3-14 (7 to 17-fold). Proliferation in 1500-3000 ppm females was strong, consistent, and dose-related. A transient increase was observed at 50 ppm in day 7 females only. Investigators concluded that test article was behaving in the manner of an enzyme inducer such as phenobarbital. NOEL in males = 250 ppm for hepatocellular cell proliferation, and 50 ppm for hepatocellular hypertrophy and liver weight increases. NOEL in females is slightly below 50 ppm for hepatocellular cell proliferation, and 250 ppm for hepatocellular hypertrophy. Males (1500-3000 ppm, treatment times of 7-14 days) had slightly elevated thyroid weights, but NOEL could not be framed exactly. Useful supplementary information, exploring shorter exposure time frames (most relevant times for proliferation) and a lower extension of dose range than Record No. 254167. Aldous, 8/31/11.

53118-0063 254167 Buesen, R., W. Kaufmann, E. Fabian, and B. van Ravenzwaay, "BAS 700 F - S-phase response study in Wistar rats: administration in the diet for 7, 28, and 91 days," BASF SE, Ludwigshafen, Germany, 2/25/10. Laboratory Study # 2009/1072498. Groups of 10 Wistar rats/sex/group were dosed in diet with BAS 700 F [Fluxapyroxad], Batch COD-001049, purity 99.2%, for 7, 28, or 91 days in a supplementary study at 0, 250, 1500, or 3000 ppm. Achieved dose (for 91-day groups) were 0, 13, 80, and 163 mg/kg/day for males, and 0, 17, 106, and 190 mg/kg/day for females. An additional 3000 ppm group was treated for 28 days, followed by a 28-day recovery period. Key parameters examined were liver weights, liver histopathology, and liver cell proliferation (7 days after implanting osmotic pumps delivering BrdU). Liver weights of both sexes were elevated at 1500 and 3000 ppm (statistically significant in all cases for relative liver weights) following 7, 28, and 91 days. High dose male liver weights were comparable to control after 28-day recovery, whereas high dose female relative liver weights were modestly but significantly elevated (11% over controls after recovery, compared to 45% over controls at day 91). Livers showed dose-related increases in incidence and degree of hepatocellular hypertrophy in all dose groups at all treatment times, but no residual effects in recovery rats. Hepatic cell proliferation was increased after 7 days in 1500 and 3000 ppm males in all zones, with the strongest response in zone 3 (centrilobular): 14- and 21-fold for

1500 and 3000 ppm, respectively. Proliferation was also increased 3-fold in 3000 ppm males in zone 3 after 91 days. In contrast, centrilobular proliferation was greatly increased in all female groups at all treatment intervals, with high dose increases of 26-fold, 14-fold, and 7-fold in females at 7, 28, and 91 days, respectively. Low dose female zone 3 responses were 4-fold, 7-fold, and 3-fold at 7, 28, and 91 days, respectively. Proliferation was not increased over controls in recovery male or female groups. Investigators concluded that test article was behaving in the manner of an enzyme inducer such as phenobarbital. Useful supplementary information. Aldous, 8/31/11.

53118-0064 254168 Buesen, R., W. Kaufmann, E. Fabian, and B. van Ravenzwaay, "BAS 700 F - S-phase response study in Wistar rats: administration in the diet for 7, 28 and 91 days," BASF SE, Ludwigshafen, Germany, 2/25/10. Laboratory Study # 2009/1072499. Ten Wistar rats/sex/group were dosed in diet with BAS 700 F [Fluxapyroxad], Batch COD-001049, purity 99.2%, for 7, 28, or 91 days in a supplementary study at 0 or 50 ppm. Mean achieved doses (for 91-day treated males and females, respectively) were 3.0 and 3.5 mg/kg/day. This study was a follow-up to supplementary study 53118-0063 254167, which employed dose levels of 250, 1500, and 3000 ppm. That study did not identify a NOEL for centrilobular proliferation in females, females being more responsive than males to centrilobular proliferation. There was no treatment effect in the present study at 50 ppm. There were statistical increases at 28 days in females in liver zones 1 and 2 in this study: these are unlikely to be toxicologically relevant because (1) Zone 1 values for the 50 ppm females at 7 days and 91 days were lower than controls, and (2) the concurrent control labeling index (LI) for Zone 2 was unusually low [less than 50% of the LI in the main supplementary study (Record No. 254167)]. Thus an overall NOEL for centrilobular proliferation is 50 ppm for females, based on this study. The NOEL for males, based on Record No. 254167, is 250 ppm. Useful supplementary data. Aldous, 8/31/11.

53118-0066 254171 Buesen, R., E. Fabian, and B. van Ravenzwaay, "BAS 700 F - Thyroid function test in Wistar rats using perchlorate discharge as a diagnostic test - administration via the diet over 2 weeks," BASF SE, Ludwigshafen, Germany, 10/19/09. Laboratory Study # 2009/1072501. Twelve rats/sex/group were dosed in diet for 2 weeks with control diet, 3000 ppm fluxapyroxad, 2000 ppm propylthiouracil (PTU: which blocks "organification" of follicular cell iodine), or 1000 ppm phenobarbital sodium (PB). On day 14, all rats received 0.5 ml (1 μ Ci) of labeled NaI (125 -I) ip. Six hrs later, 6 of these rats/sex/group received KClO₄ ip (amount not specified: function apparently to block iodide transfer across thyroid follicular cell membrane): remaining rats received saline blank. Rats were sacrificed 2.5 min after KClO₄ or saline treatment. Investigators calculated thyroid weight, specific radioactivity in blood and in thyroid, and the ratio of 125 -I of thyroid to blood. Fluxapyroxad behaved similarly to PB, with thyroid weights increased up to 50% and a similar increase in specific radioactivity in thyroid. PTU elicited a 4-5-fold increase in thyroid weights, with a profound reduction of specific radioactivity in thyroid (only about 20% of control). KClO₄ further reduced 125 -I label in thyroids of PTU rats (to 6-11% of controls), with no effect on PB or fluxapyroxad. Results showed that fluxapyroxad behaves similarly to PB in the outcomes assayed, and that fluxapyroxad does not inhibit thyroid hormone formation in the manner of PTU. Useful supplementary information. Aldous, 4/5/11.

53118-0064 254169 Doi, A. M., "Evaluation of a mode of action for liver tumor induction by BAS 700 F," [not a laboratory study, but "performing facility" was BASF in Research Triangle Park, NC], 2/17/10. This author summarized key points of the above studies (mainly the rat

combined study, plus the studies in the present “Mechanistic Studies” section of this Summary of Toxicology Data, concluding on p. 17 that “The overall weight of evidence strongly supports a mitogenic MoA with clear thresholds for development [of] liver tumors in rats.” This is not a “study” for DPR Data Review Group to evaluate, but is a potential useful overview for liver and thyroid cancer-associated risk assessment. No DPR worksheet. Aldous, 8/29/11.

IMMUNOTOXICITY

**53118-0060 254163 Kaspers, U., V. Strauss, S. Groeters, E. Fabian, and B. van Ravenzwaay, “BAS 700 F - Immunotoxicity study in male C57BL/6 J Rj mice; administration in the diet for 4 weeks,” BASF SE, Ludwigshafen, Germany, Oct. 8, 2009. Laboratory Study # 2009/1072494, Project. No. 43S0683/05105. Groups of 8 male mice/sex/group were dosed in diet with fluxapyroxad (Batch COD-001049, purity 99.2%) for 28 days at 0, 500, 2000, or 6000 ppm (0, 106, 450, and 1323 mg/kg/day, respectively). Positive controls received 12 mg/kg/day cyclophosphamide (gavage) for 4 weeks. Mice were immunized with SRBC ip on day 23 to assess T-cell antibody response [by anti-SRBC (sheep blood RBC) IgM ELISA methods]. Sacrifice was on day 29. Natural killer (NK) cell activity was assessed for leukocytes derived from spleens by determining damage to YAC lymphoma cells by flow cytometry after staining for damaged YAC cells. Flow cytometry was used to differentiate sub-populations of lymphocytes, with aid of stain-labeled antibodies to mouse CD3ε, CD4, CD8a, NK-1.1, and CD19. Fluxapyroxad was negative for all parameters. Cyclophosphamide greatly reduced T-cell antibody response, markedly reduced all sub-populations of lymphocytes assayed, and sharply reduced B:T ratios. Cyclophosphamide caused a profound decrease in T-cell antibody response, but no effect on NK cell activity. Acceptable, with no adverse effects. Aldous, Oct. 6, 2011.

TOXICITY STUDIES ON TECHNICAL IMPURITIES (generally no DPR worksheets needed)

53118-0067 254189 Schulz, M., and Landsiedel, R., “Reg. No. 5425764 (Technical impurity of BAS 700F) - *Salmonella typhimurium* / *Escherichia coli* reverse mutation assay (standard plate test and preincubation test),” BASF AG, Ludwigshafen, Germany, 1/18/08, Laboratory Study # 2007/1054385. There were no consistent increases in revertants. A marginal (2 x) increase in the standard plate test with TA 1535 without S-9 at 500 µg/plate was not repeated in a standard plate test nor in the pre-incubation test. Aldous, no treatment effects, and no DPR worksheet, July 6, 2011.

53118-0067 254190 Schulz, M., and Landsiedel, R., “Reg. No. 5425764 (Technical impurity of BAS 700F) - *in vitro* gene mutation test in CHO cells (HPRT locus assay),” BASF SE, Ludwigshafen, Germany, Nov. 4, 2008, Laboratory Study # 2008/1068013. There were no treatment effects indicated in either of two separate experiments with or without S-9. Aldous, no DPR worksheet, July 6, 2011.

53118-0067 254191 Schulz, M., and Landsiedel, R., “Reg. No. 5425764 (Technical impurity of BAS 700F) - micronucleus test in bone marrow cells of the mouse,” BASF AG, Ludwigshafen, Germany, 1/17/08, Laboratory Study # 2008/1002421. There were no treatment effects indicated in either of two separate experiments, the first experiment with dose levels of 0, 500, 1000, and

2000 mg/kg Reg. No. 5425764 (purity 99.9%) with a 24-hr sacrifice interval, nor at 0 and 2000 mg/kg with a 48-hr period. Aldous, no DPR worksheet, Sept. 6, 2011.

53118-0068 254192 Schulz, M., and Landsiedel, R., "Reg. No. 5356469 (Technical impurity of BAS 700F) - *Salmonella typhimurium* / *Escherichia coli* reverse mutation assay (standard plate test and preincubation test)," BASF AG, Ludwigshafen, Germany, 1/28/08, Laboratory Study # 2007/1054448. There were no remarkable, dose-related, or consistent increases in revertants. Aldous, no treatment effects, and no DPR worksheet, 7/7/11.

53118-0068 254193 Schulz, M., and Landsiedel, R., "Reg. No. 5356469 (Technical impurity of BAS 700F) - *in vitro* gene mutation test in CHO cells (HPRT locus assay)," BASF SE, Ludwigshafen, Germany, Nov. 4, 2008, Laboratory Study # 2008/1068014. There were no treatment effects indicated in either of two separate experiments with or without S-9. Aldous, no DPR worksheet, 7/7/11.

53118-0068 254194 Schulz, M., and Landsiedel, R., "Reg. No. 5356469 (Technical impurity of BAS 700F) - micronucleus test in bone marrow cells of the mouse (including amendment No. 1)," BASF SE, Ludwigshafen, Germany, 12/19/08 (amended), Laboratory Study # 2008/7020156. There were no treatment effects indicated in either of two separate experiments, the first experiment with dose levels of 0, 500, 1000, and 2000 mg/kg fluxapyroxad with a 24-hr sacrifice interval, nor at 0 and 2000 mg/kg with a 48-hr period. Aldous, no DPR worksheet, 7/7/11.

53118-0069 254199 Schulz, M., and Landsiedel, R., "3',4',5'-Trifluoro-biphenyl-2-ylamine: *Salmonella typhimurium* / *Escherichia coli* reverse mutation assay (standard plate test and preincubation test)," BASF SE, Ludwigshafen, Germany, Oct. 1, 2009, Laboratory Study # 2009/1072516. There were no remarkable alterations in revertants. Aldous, no treatment effects, and no DPR worksheet, 7/7/11.

53118-0069 254200 Schulz, M., and Landsiedel, R., "3',4',5'-Trifluoro-biphenyl-2-ylamine - *in vitro* gene mutation test in CHO cells (HPRT locus assay)," BASF SE, Ludwigshafen, Germany, 9/22/09, Laboratory Study # 2009/1072518. There were no treatment effects indicated in either of two separate experiments with or without S-9. Aldous, no DPR worksheet, 7/7/11.

53118-0069 254201 Schulz, M., and Landsiedel, R., "3',4',5'-Trifluoro-biphenyl-2-ylamine: micronucleus test in bone marrow cells of the mouse," BASF SE, Ludwigshafen, Germany, Oct. 2, 2009, Laboratory Study # 2009/1072517. There were no treatment effects indicated in either of two separate experiments, the first experiment with dose levels of 0, 15, 30, and 60 mg/kg of 3',4',5'-trifluoro-biphenyl-2-ylamine with a 24-hr sacrifice interval, nor at 0 and 60 mg/kg with a 48-hr period. Micronuclei in the 60 mg/kg group with the 48-hr period were significantly elevated over concurrent controls (0.8 vs. 1.8 micronuclei per thousand PCE's), but was similar to mean historical control values, and identical to a control value reported in the same month by these investigators (DPR Record No. 254216). Toxicity was evident at all dose levels tested: with piloerection at 15 mg/kg, and additionally hunched posture and "reduced general condition" at 30-60 mg/kg, and "necrotic tail tip" in all 60 mg/kg mice at 48 hrs. Aldous, no DPR worksheet, 9/6/11.

TOXICITY STUDIES ON METABOLITES

BASF Reg. No. 5435595

NOTE: This test article is designated as M700F002 in fluxapyroxad metabolism studies. IUPAC name: 3-(difluoromethyl)-1H-pyrazole-4-carboxylic acid. Purity = 99.3% (from Record No. 254209, p. 14).

53118-0074 254209 Cords, S.-M., and E.-M. Lammer, "Reg. No. 5435595 (Metabolite of BAS 700F) - acute oral toxicity study in rats," Bioassay Labor Für Biologische Analytic GmbH, Heidelberg, Germany. Six female Wistar rats were dosed once by gavage at 2000 mg/kg. No rats died. Clinical signs of "impaired general state," dyspnea, and piloerection were observed in 2/6 rats. LD₅₀ (F) > 2000 mg/kg. Toxicity Category III. Useful data, no DPR worksheet, Aldous, 8/24/11.

53118-0074 254210 Kaspers, U., V. Strauss, S. Gröters, E. Fabian, and B. van Ravenzwaay, "Reg. No. 5435595 (Metabolite of BAS 700F) - Repeated dose 28-day oral toxicity study in Wistar rats; administration in the diet," BASF SE, Ludwigshafen, Germany, Dec. 8, 2008. Five Wistar rats/sex/dose were dosed in diet at 0, 1500, 5000, or 15000 ppm for 4 weeks. There were no treatment-related clinical signs, no changes in hematology or clinical chemistry, nor changes in necropsy or histopathology. Thus the NOEL is 15000 ppm, estimated to be 1165 mg/kg/day for males, and 1253 for females. Useful data, no DPR worksheet, Aldous, 8/24/11.

53118-0075 254211 Kaspers, U., V. Strauss, S. Gröters, E. Fabian, and W. Mellert, "Reg. No. 5435595 (Metabolite of BAS 700F) - Repeated dose 90-day oral toxicity study in Wistar rats; administration in the diet," BASF SE, Ludwigshafen, Germany, 5/13/09. Dietary levels were adjusted weekly to achieve target dose levels of 0, 100, 300, or 1000 mg/kg/day. There were 10 rats/sex/group. Investigators assessed clinical signs, and at or near to termination, also hematology, clinical chemistry, urinalysis, ophthalmology, necropsy, and histopathology. No treatment-related effects were observed. NOEL = 1000 mg/kg/day for both sexes. Useful data, no DPR worksheet, Aldous, 8/24/11.

53118-0076 254212 Schneider, S., E. Fabian, and W. Mellert, "Reg. No. 5435595 (Metabolite of BAS 700F) - Prenatal developmental toxicity study in New Zealand White rabbits - oral administration (gavage)," BASF SE, Ludwigshafen, Germany, Oct. 13, 2009. Rabbits received gavage treatments of 0, 100, 300, and 1000 mg/kg/day from gestation days 6-28 in a standard developmental toxicity study. Incidences of abortions, and premature deaths were elevated at 1000 mg/kg/day. Significantly reduced food consumption, absent or reduced defecation, and occasional stomach ulceration at necropsy were major indicators of poor general state at the high dose. Body weight gain in surviving high dose does was significantly reduced. Developmental toxicity was not evident at any dose. Maternal NOEL = 300 mg/kg/day (mortalities and clinical signs). Developmental NOEL = 1000 mg/kg/day (no treatment-related effects at HDT). Useful data. No DPR worksheet is warranted at this time. Aldous, 10/10/11.

53118-0077 254213 Schulz, M., and Landsiedel, R., "Reg. No. 5435595 (Metabolite of BAS 700F) - *Salmonella typhimurium* / *Escherichia coli* reverse mutation assay (standard plate test and preincubation test)," BASF AG, Ludwigshafen, Germany, 11/21/07, Laboratory Study # 2007/1051931. There were no increases in revertants. Aldous, no DPR worksheet, 7/7/11.

53118-0077 254214 Schulz, M., and Landsiedel, R., "Reg. No. 5435595 (Metabolite of BAS 700F) - *in vitro* gene mutation test in CHO cells (HPRT locus assay)," BASF SE, Ludwigshafen, Germany, 7/14/08, Laboratory Study # 2008/1014199. There were no treatment effects indicated in either of two separate experiments without S-9 or three separate experiments with S-9. Aldous, no DPR worksheet, 7/7/11.

53118-0077 254215 Schulz, M., and Landsiedel, R., "Reg. No. 5435595 (Metabolite of BAS 700F) - *in vitro* chromosomal aberration assay in V79 cells," BASF SE, Ludwigshafen, Germany, March 10, 2008, Laboratory Study # 2008/1002741. Dose levels from 100 to 1600 µg/ml were employed, with hours of exposure/preparation period without S-9 of 4/18 (two experiments), 18/18, and 18/28. There were no significant elevations without S-9 due to the tested metabolite, although 800-1600 µg/ml groups exceeded reported historical control values. Concurrent control was relatively high. The same dose levels were used with S-9, with hours of exposure/preparation period of 4/18 and 4/28. There were statistically significant elevations with S-9 in metabolite groups, but these were within reported historical control values, lacked dose-response, and appear to be negative. Investigators justifiably considered the study as negative. Aldous, no DPR worksheet, 7/7/11.

53118-0077 254216 Schulz, M., and Landsiedel, R., "Reg. No. 5435595 (Metabolite of BAS 700F): micronucleus test in bone marrow cells of the mouse ," BASF SE, Ludwigshafen, Germany, Oct. 5, 2009. Laboratory Study # 2009/1072508. Dose levels of 0, 375, 750, and 1500 mg/kg Reg. No. 5435595 (99.3% purity) were administered to 5 NMRI mice/group, 24 hrs before sacrifice. Additional groups at 0 and 1500 mg/kg were evaluated 48 hrs after dosing. There were no clinical signs in this range, however 2000 mg/kg had been shown to elicit major clinical signs for at least 48 hrs, hence maximum dose for final study was justified. There were no treatment-related increases in micronuclei. Useful data, no DPR worksheet, Aldous, 9/6/11.

53118-0077 254217 Fabian, E., and Landsiedel, R., "Reg. No. 5435595 (Metabolite of BAS 700F): study on the kinetics in mice, BASF SE, Ludwigshafen, Germany, Oct. 9, 2009. Laboratory Study # 2009/1098042. This study related to the mouse micronucleus study, and confirmed that a high dose (1000 mg/kg) reached mean concentrations in bone marrow at 5 hrs which were about double that of blood cells, with plasma residues intermediate between blood cells and marrow. Thus a meaningful dose was received in the marrow for a valid micronucleus study. Useful data, no DPR worksheet, Aldous, 7/7/11.

BASF Reg. No. 5069089

NOTE: This test article is a very minor metabolite in the rat. It is CAS No. 176969-34-9: 1H-Pyrazole-4-carboxylic acid, 3-(difluoromethyl)-1-methyl- [99.2% purity] (see Document No. 53118-0072, Record No. 254204, p. 551. This substance is designated as M700F001 in the metabolism studies of this Summary.

53118-0070 254202 Cords, S.-M., and E.-M. Lammer, "Reg. No. 5069089 (Metabolite of BAS 700F): acute oral toxicity study in rats," Bioassay Labor Fuer Biologische Analytic GmbH, Heidelberg, Germany, Laboratory Study No. 2009/1072502. Six female Wistar rats were dosed once with Reg. No. 5069089 (purity 99.2%) by gavage at 2000 mg/kg. One rat had general clinical signs during hours 4-5 after dosing: "impaired general state," dyspnea, and piloerection.

Reduced feces were observed in 2 rats. There were no deaths. LD₅₀ (F) > 2000 mg/kg. Toxicity Category III. Useful data, no DPR worksheet, Aldous, 9/6/11.

53118-0071 254203 Kaspers, U., V. Strauss, S. Groeters, E. Fabian, and B. van Ravenzwaay, “Reg. No. 5069089 (Metabolite of BAS 700F) - Repeated dose 90-day oral toxicity study in Wistar rats; administration in the diet,” BASF SE, Ludwigshafen, Germany, Oct. 8, 2009. Report No. 50S0451/07119. (Reg. No. 5069089, Batch No. L80-68, purity 99.2%). This study indicated no remarkable findings up to a dose level of 1000 mg/kg/day in the report summary. No DPR worksheet is warranted at this time. Aldous, 8/23/11.

53118-0072 254204 Schneider, S., E. Fabian, and W. Mellert, “Reg. No. 5069089 (Metabolite of BAS 700F) - Prenatal developmental toxicity study in New Zealand White rabbits - oral administration (gavage),” BASF SE, Ludwigshafen, Germany, Oct. 14, 2009. Report No. 40R0451/07118. Reg. No. 5069089 (Batch No. L80-68, purity 99.2%). This study indicated no remarkable findings in the report summary up to the highest dose tested (250 mg/kg/day). Some clinical signs reported in the associated pilot study included reduced food consumption at 250 mg/kg/day, and occasional stomach erosions, and mortalities and/or abortion at 500 to 1000 mg/kg/day. Tables of fetal data from the primary study showed no treatment-related findings. No DPR worksheet is warranted at this time. Aldous, 8/25/11.

53118-0073 254205 Schulz, M. and R. Landsiedel, “Reg. No. 5069089 (Metabolite of BAS 700F) - *Salmonella typhimurium* / *Escherichia coli* reverse mutation assay (standard plate test and preincubation test),” BASF SE, Ludwigshafen, Germany, Sept. 7, 2009. Reg. No. 5069089 (Batch No. L80-68, purity 99.2%). Report No. 40R0451/074195. This test was negative, employing concentrations up to 5000 µg/plate (or 2x or 4x reduction thereof if limited by cytotoxicity). No DPR worksheet is warranted at this time. Aldous, 8/24/11.

53118-0073 254206 Schulz, M. and R. Landsiedel, “Reg. No. 5069089 (Metabolite of BAS 700F) - *in vitro* gene mutation test in CHO cells (HPRT locus assay) (Including Amendment No. 1),” BASF SE, Ludwigshafen, Germany, July 9, 2009, Amended Sept. 1, 2009. Report No. 50M0451/074157. Reg. No. 5069089 (Batch No. L80-68, purity 99.2%). Dose levels up to 2000 µg/mL (about 11.4 mM, meeting limit test) were not limited by toxicity. Primary test used 250, 500, 1000, and 2000 µg/mL with 4 hr or 24 hr exposure periods, each with and without S-9. Results were negative. No DPR worksheet is warranted at this time. Aldous, 8/24/11.

53118-0073 254207 Schulz, M. and R. Landsiedel, “Reg. No. 5069089 (Metabolite of BAS 700F) - *in vitro* chromosome aberration assay in V79 cells,” BASF SE, Ludwigshafen, Germany, 8/31/09. Report No. 32M0451/074158. Dose levels up to 2000 µg/mL of Reg. No. 5069089 (Batch No. L80-68, purity 99.2%) were employed for exposure/(time to harvest) periods of 4/18, 18/18, or 18/28 hrs without S-9, and 4/18, and 4/28 hrs with S-9. All test article groups were negative. No DPR worksheet is warranted at this time. Aldous, 8/24/11.

53118-0073 254208 Schulz, M. and R. Landsiedel, “Reg. No. 5069089 (Metabolite of BAS 700F) - micronucleus test in bone marrow cells of the mouse ,” BASF SE, Ludwigshafen, Germany, Oct. 5, 2009. Report No. 26M0451/074181. Investigators tested 500, 1000, or 2000 mg/kg of Reg. No. 5069089 (Batch No. L80-68, purity 99.2%) to 5 male NMRI mice/group with a 24-hr sacrifice time, or 2000 mg/kg with a 48-hr sacrifice time. This treatment did not increase micronuclei. No DPR worksheet is warranted at this time. Aldous, 8/24/11.

BASF Reg. No. 5621781

NOTE: This test article was characterized in the report as a metabolite of fluxapyroxad, (designated M700F007 in the metabolism studies) purity 99.4%.

53118-0078 254218 Cords, S.-M., and E.-M. Lammer, "Reg. No. 5621781 (Metabolite of BAS 700F): acute oral toxicity study in rats," Bioassay Labor Fuer Biologische Analytic GmbH, Heidelberg, Germany, Laboratory Study No. 2009/1084176, Oct. 2, 2009. Three female Wistar rats were dosed once at 2000 mg/kg of Reg. No. 5621781, Batch L81-108, purity 99.4%. All of these died: 2 of them within 5 hours after dosing. All had multiple clinical signs such as "poor general state," dyspnea, ataxia, twitching, staggering, and piloerection. Six females were dosed once with 500 mg/kg. Of these, one showed some of the above signs during hrs 4-5: all others were without unusual clinical signs. Necropsy was not remarkable in any group. Thus 500 mg/kg < LD₅₀ (F) < 2000 mg/kg. Toxicity Category III. Useful data, no DPR worksheet, Aldous, 8/25/11.

BASF Reg. No. 5570265

NOTE: This test article was characterized in Document No. 53118-0083, Record No. 254227, (page 29) as M700F048. It is the β -glucuronide of fluxapyroxad, the glucuronide displacing the N-methyl group of an otherwise intact fluxapyroxad molecule. Most of the glucuronides derived from the a.i. also had hydroxylation on one of the phenyl rings (Document No. 53118-0058, Record No. 254161) so that this is not one of the most abundant metabolites.

53118-0079 254219 Cords, S.-M., and E.-M. Lammer, "Reg. No. 5570265 (Metabolite of BAS 700F): acute oral toxicity study in rats," Bioassay Labor Fuer Biologische Analytic GmbH, Heidelberg, Germany, Laboratory Study No. 2009/1018496, 7/14/09. Six female Wistar rats were dosed once at 2000 mg/kg of Reg. No. 5570265, Batch No. L81-104, purity 93.7%. No deaths occurred. Necropsy was not remarkable in any group. Some clinical signs were observed in 4 rats, primarily within the first 3 hrs or up to a maximum of 3 days. Signs included diarrhea, impaired general state, piloerection, and dyspnea. LD₅₀ (F) > 2000 mg/kg. Toxicity Category III. Useful data, no DPR worksheet, Aldous, 8/25/11.

53118-0080 254220 Kaspers, U., V. Strauss, S. Groeters, E. Fabian, and B. van Ravenzwaay, "Reg. No. 5570265 (Metabolite of BAS 700F) - Repeated dose 28-day oral toxicity study in Wistar rats; administration in the diet," BASF SE, Ludwigshafen, Germany, Oct. 8, 2009. Laboratory Study # 2009/1072510. Ten Wistar rats/sex/dose were dosed in diet with Reg. No. 5570265 (93.7% purity) for 28 days at nominal 0, 50, 200, or 1000 mg/kg/day. High dose findings, normally in both sexes, included reduced body weight gains, elevated liver weights (absolute and relative), reduction of bile acids in serum, and increase in urinary crystals (significant in females only). In the histopathological examination, 8 males and 4 females at 1000 mg/kg/day demonstrated minimal hepatocellular centrilobular hypertrophy in the liver. In addition, there was a dose-related reduction in total bilirubin at 200 to 1000 mg/kg/day in both sexes. Useful data, no DPR worksheet, Aldous, 9/6/11.

53118-0081 254221 Schneider, S., E. Fabian, and W. Mellert, "Reg. No. 5570265 (Metabolite of BAS 700F) - Prenatal developmental toxicity study in New Zealand White rabbits - oral administration (gavage)," BASF SE, Ludwigshafen, Germany, 2/22/10. Report No. 40R0008/09008. Dose levels were 0, 10, 30, and 100 mg/kg/day of metabolite Reg. No. 5570265 (Batch L81-124, purity 96.1%), administered by gavage on gestation days 6-28. Maternal toxicity at 100 mg/kg/day was reflected by decreased food consumption and decreased body weight gain during the treatment period, and abortions usually tied to clinical signs of "no defecation." There were no definitive fetal effects. No DPR worksheet is warranted at this time. Aldous, 8/25/11.

53118-0082 254222 Schulz, M. and R. Landsiedel, "Reg. No. 5570265 (Metabolite of BAS 700F) - *Salmonella typhimurium* / *Escherichia coli* reverse mutation assay (standard plate test and preincubation test)," BASF SE, Ludwigshafen, Germany, Sept. 21, 2009. Report No. 40M0008/094079. This test was negative, employing concentrations in 2x steps, not limited by solubility and generally not by toxicity up to 5500 µg/plate of Reg. No. 5570265 (Batch L81-124, purity 93.7%). No DPR worksheet is warranted at this time. Aldous, 8/25/11.

53118-0082 254223 Schulz, M. and R. Landsiedel, "Reg. No. 5570265 (Metabolite of BAS 700F) - *in vitro* gene mutation test in CHO cells (HPRT locus assay)," BASF SE, Ludwigshafen, Germany, 8/31/09. Report No. 50M0008/094054. Dose levels up to 500-750 µg/mL of Reg. No. 5570265 (Batch No. L81-104, purity 93.7%) were usable without S-9, and up to 1000-1250 µg/mL with S-9, limited by cytotoxicity. Test article was not mutagenic. No DPR worksheet is warranted at this time. Aldous, 8/25/11.

53118-0082 254224 Schulz, M. and R. Landsiedel, "Reg. No. 5570265 (Metabolite of BAS 700F) - *in vitro* chromosomal aberration assay in V79 cells," BASF SE, Ludwigshafen, Germany, Oct. 2, 2009. Report No. 32M0008/094198. Exposure/(time to harvest) periods of 4/18, 18/18, or 18/28 hrs were used without S-9, and 4/18, and 4/28 hrs with S-9. Dose levels up to 375 to 750 µg/mL of Reg. No. 5570265 (Batch No. L81-124, purity 96.1%) were maximum usable levels without S-9, and dose levels up to 1000 to 1200 µg/mL were usable with S-9, based on cytotoxicity. All test article groups without S-9 were negative. The top readable dose levels with S-9 (1000 to 1200 µg/mL) elicited statistically **increased chromosomal aberrations** in two trials at 4/28 [Exposure/(time to harvest)] hrs only. [There were no increases at the next lower dose levels of 750 to 800 µg/mL in those 2 trials]. Result is **positive** at limits based on cytotoxicity. No DPR worksheet is warranted at this time. Aldous, 8/25/11.

53118-0082 254225 Schulz, M. and R. Landsiedel, "Reg. No. 5570265 (Metabolite of BAS 700F) - micronucleus test in bone marrow cells of the mouse ," BASF SE, Ludwigshafen, Germany, Oct. 5, 2009. Report No. 26M0008094005. Investigators tested 500, 1000, or 2000 mg/kg of Reg. No. 5570265 (Batch No. L81-124, purity 96.1%) to 5 male NMRI mice/group with a 24-hr sacrifice time, or 2000 mg/kg with a 48-hr sacrifice time. There was a statistically significant increase in micronuclei for the 1000 mg/kg mice with a 24-hr sacrifice time: all other test groups were negative. Investigators considered the study to be negative, considering lack of dose-response, and noting that the significant value was well within historical range. No DPR worksheet is warranted at this time. Aldous, 8/25/11.

53118-0083 254226 Schulz, M. and R. Landsiedel, "Reg. No. 5570265 (Metabolite of BAS 700F): *in vivo* unscheduled DNA synthesis (UDS) assay in rat hepatocytes," BASF AG,

Ludwigshafen, Germany, 10/21/09 (as amended). Report No. 80M0008/094199. Laboratory Study # 2009/7006262. Groups of 3 male Wistar rats/group were dosed by gavage with 0, 1000, or 2000 mg/kg of Reg. No. 5570265, purity 96.1%, (Batch No. L81-124), or by gavage with 50 mg/kg 2-acetylaminofluorene (positive control) with sampling times of 3 hrs or 14 hrs to sacrifice. Net nuclear grain counts were unaffected by test article (negative for UDS). Positive control was functional. Useful data. No DPR worksheet is warranted at this time. Aldous, 8/26/11.

53118-0083 254227 Fabian, E., and Landsiedel, R., "Reg. No. 5570265 (Metabolite of BAS 700F): study on the kinetics in mice, BASF SE, Ludwigshafen, Germany, Oct. 9, 2009. Laboratory Study # 2009/1098044. This study related to the mouse micronucleus study in Record No. 254225 (above), and confirmed that a high dose (1000 mg/kg) of Reg. No. 5570265 (Batch No. L81-104, purity 93.7%) reached mean concentrations in bone marrow at 5 hrs which were over twice that of blood cells, and comparable to plasma levels. Thus the dose received in the marrow was suitable for the micronucleus study. Useful data, no DPR worksheet, Aldous, 8/26/11.

53118-0083 254228 Griesser, M., "Excretion and metabolism of ¹⁴C-M700F048 after oral administration in rats," BASF SE, Limburgerhof, Germany, 9/22/09. Report No. 366577. This test article is Reg. No. 5570265, Batch No. L81-104, purity 93.7%. Four Wistar rats/sex were dosed once by gavage with 7.5 mg/kg of ¹⁴C-M700F048 (Batch No. 957-1019, radiochemical purity 98.3%) with label in phenyl group adjacent to amide. Excreta were evaluated for 7 days. Urine comprised 2.4% and 6.8% of administered label in males and females, respectively. Main components in the urine were characterized, and were (highest component first): (1) M700F050 (cleavage of N-glucuronide of Reg. No. 5570265 followed by O-glucuronidation somewhere on one of the phenyl rings), (2) M700F009 (cleavage of N-glucuronide of Reg. No. 5570265 followed by hydroxylation somewhere on one of the phenyl rings) - this was a major metabolite of fluxapyroxad, and (3) small but measurable amounts of Reg. No. 5570265. In both sexes, 26-30% of administered dose in fecal residues was comprised of administered Reg. No. 5570265, and about equal amounts were M700F009. The other common metabolite (15-16% of administered dose) was M700F008 (the simple cleavage of N-glucuronide from Reg. No. 5570265). Findings were consistent with behavior of fluxapyroxad in the main metabolism study (Record No. 254161). Useful supplementary data. No DPR worksheet. Aldous, 8/26/11.