

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Mandipropamid

Chemical Code # 5961, Tolerance # 53030, SB 950 # NA

April 17, 2008

I. DATA GAP STATUS

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

Toxicology one-liners are attached.

All record numbers through 230467 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T080417, H. Green

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

COMBINED, RAT

**53030-0115 230434, "NOA446510: Two Year Chronic Toxicity and Carcinogenicity Study in Rat, Final Report", (P.J. Pinto, Syngenta Central Toxicology Laboratory, Macclesfield, Cheshire, UK., Report No. CTL/PR1274 REG, 9 November 2005). 52 Alpk:AP_iSD (Wistar-derived) rats per sex per group received NOA446510 (96.5%) in the diet at 0 (CT1 diet), 50, 250, and 1000 ppm for 2 years. Additional groups of 12 animals per sex per group were necropsied at 12 months. Mean NOA446510 dose values during 104 weeks, based on nominal treatment levels, were 3.0, 15.2, and 61.3 mg/kg/day for males and 3.5, 17.6, 69.7 mg/kg/day for females at 50, 250, and 1000 ppm respectively. Male group mean bodyweight and bodyweight gain were significantly reduced at 1000 ppm between weeks 4 through 15 (~4%) and between weeks 67 and 103 (up to 7%). Male low and mid dose groups and female bodyweights were not affected. Significant hematology changes included decreased mean cell volume and mean cell hemoglobin for high dose males and females at weeks 14, 27, 53, and 79 relative to controls. Mean cell hemoglobin was also reduced ($p < 0.05$) for females at week 105. Statistically significant blood clinical chemistry changes at 1000 ppm included: increased gamma glutamyl transferase activity in males at weeks 53, 79, and 105; decreased alkaline phosphatase activity at weeks 14 and 27 in males and at weeks 14, 53, and 105 in females (decreases (ns) were also noted for females at weeks 27 and 79); and increased plasma albumin in males at weeks 14, 27, and 53. At week 53, group mean absolute liver weights were significantly increased for males (10%) and females (14%) at 1000 ppm and for mid dose females (10%) compared to controls. Group mean relative liver weights were also increased (statistical analysis was not performed) for males (8%) and females (14%) at 1000 ppm and for mid dose females (9%). At week 105, at the high dose level, significant increases in female group absolute liver weights (11%) were noted vs controls, while male group mean liver weights were increased (ns) 6%. Group mean relative liver weights at 1000 ppm were increased 7.5% for males and 11% for females. Significant increases in group mean absolute kidney weights were noted for mid (6%) and high dose females (7%) at week 53 compared to controls (relative kidney weights were increased 4% and 7% respectively). Week 105 kidney weights were unremarkable. The only treatment related macroscopic findings were noted in kidneys of high dose males at week 105 (enlargement, roughened surface, and cysts). Microscopy revealed an increase in the severity of chronic progressive nephropathy at 1000 ppm in kidneys of males along with an increased incidence of renal osteodystrophia fibrosa in the femur and sternum, and hyperplasia of the parathyroid (osteo-renal syndrome) at week 105. Chronic NOEL = 250 ppm (M: 15.3 mg/kg/day; F: 17.6 mg/kg/day) (reduced bodyweight/bodyweight gain in males, hematology and blood chemistry changes in both sexes, and kidney microscopy in males). No increase in neoplastic lesions. No adverse effects. Acceptable. (Green and Leung, 4/16/08).

CHRONIC TOXICITY, RAT

See Combined Rat, above.

CHRONIC TOXICITY, DOG

0113; 230432; "NOA446510: 1 Year Oral Toxicity Study in Dogs" (Brammer, A., Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Laboratory Project ID: Report Number PD1273-REG Syngenta Number T004622-02, 10/7/05). 870.4100. NOA 446510 (technical) (Batch reference number SEZ2BP007, purity = 96.5%) was administered by gelatin capsules to 4 beagle dogs per sex per dose at dose levels of 0 (empty gelatin capsules), 5, 40, and 400 mg/kg/day daily for at least 1 year. No mortalities occurred. No treatment-related clinical signs were observed. A treatment-related decrease in adjusted mean body weight (determined by analysis of covariance) was observed in both sexes at 400 mg/kg/day. Treatment-related increases in the adjusted mean plasma alkaline phosphatase level at 40 and 400 mg/kg/day and adjusted mean alanine aminotransferase level at 400 mg/kg/day (determined by analysis of covariance) were observed in both sexes. A treatment-related increase in liver weight adjusted to body weight (determined by analysis of covariance) was observed in both sexes at 400

mg/kg/day. Microscopic examination revealed treatment-related pigmentation in the liver (consistent with porphyrin) in both sexes at 40 and 400 mg/kg/day. **No adverse effects.** NOEL (M/F) = 5 mg/kg/day based on an increase in liver weight, elevation in liver enzymes, and pigment deposition in the liver. **Acceptable.** (Corlett and Leung, 03/27/08).

ONCOGENICITY, RAT

See Combined Rat, above.

ONCOGENICITY, MOUSE

**53030-0114 230433, "NOA446510: 80 Week Carcinogenicity Study in Mice, Final Report", (G.M. Milburn, Syngenta Central Toxicology Laboratory, Macclesfield, Cheshire, UK., Report No. PM1275-REG, 11 November 2005). 50 C57BL/10J_rCD-1 mice per sex per group received NOA446510 (96.5%) in the diet at 0 (CT1 diet), 100, 500, and 2000 ppm for 80 weeks. Based on nominal dietary levels, the mean NOA446510 intake during 80 weeks was 10.6, 55.2, and 222.7 mg/kg/day for males and 13.2, 67.8, and 284.6 mg/kg/day for females at 100, 500, and 2000 ppm respectively. At 2000 ppm, reductions in group mean bodyweight (statistically significant for females for weeks 15 through 81) and bodyweight gain (statistically significant for both sexes for weeks 15 through 81) were noted for males (4% and 10% respectively) and females (7% and 10% to 12% respectively). Food consumption was not effected by treatment. Group mean absolute liver weights were significantly increased for males (15%) and females (8.8%) at 2000 ppm compared to controls and for males (11.6%) at 500 ppm (based on group mean adjusted organ weight which were corrected for intergroup differences in group mean terminal bodyweight calculated statistically using analysis of covariance). Group mean relative liver weights were increased 13.5% (males) and 10.6% (females) vs controls at the high dose and 11.3% for males at 500 ppm (no statistical analysis of relative organ weights). Group mean absolute kidney weights were increased for females at the mid (18.3%) and high dose levels (14.9%) while group mean relative kidney weights were 16.3% and 19.5% higher for mid and high dose females respectively. Group mean absolute spleen weights were decreased for high dose males (36%) and females (23%) and, for mid dose females (23%). Group mean relative spleen weights were 18% (males) and 16% (females) lower at the high dose and 35% lower for mid dose females vs controls. The incidence of cystic kidneys was increased for treated females with 0, 2, 4, and 4 at 0, 100, 500, and 2000 ppm, respectively. Microscopy was unremarkable. Chronic NOEL = 500 ppm (reduced bodyweight and bodyweight gain). Carcinogenicity NOEL = 2000 ppm. No adverse effect. Acceptable. (Green and Leung, 4/17/08).

REPRODUCTION, RAT

**53030-0111 230430, "NOA446510: Multigeneration Reproduction Toxicity Study in Rats, Final Report", (G.M. Milburn, Syngenta Central Toxicology Laboratory, Macclesfield, Cheshire, UK., Report No. RR0990-REG, 11 November 2005). 26 Alpk:AP_rSD (Wistar-derived) rats per sex per group received NOA446510 (96.5%) in the diet at 0 (untreated diet), 50, 250, and 1500 ppm through 2 generations with 1 litter in the first generation and 2 in the second. Mean dose received during the premating interval for F0 males was 4.4, 21.8, and 138.5 mg/kg/day; and 4.7, 23.4, and 140.4 mg/kg/day for F0 females; 4.9, 23.9, 154.1 mg/kg/day for F1 males and 5.2, 25.6, 156.0 mg/kg/day for F1 females at 50, 250, and 1500 ppm respectively. Group mean bodyweight for F1 parents at the high dose level was significantly reduced relative to controls throughout the premating period. Treatment-related effects on F0 bodyweights were not indicated. Group mean relative liver and kidney weights were increased at 1500 ppm for F0 and F1 males and females. Sperm parameters, gross pathology, and histopathology for F0 and F1 animals were unremarkable. At 1500 ppm, statistical reductions in pups weights relative to controls were recorded for F1a and F2b pups from lactation day 15 onwards (approximate time pups began consuming treated diet). Equivocal reductions (not significant) were indicated for F2a pup weights at the high dose for the same time intervals. Group mean relative liver weights were increased for F1a, F2a, and F2b pups at 1500 ppm compared to controls and group mean relative brain weights were increased for F1a males and females at the high dose. No macroscopic abnormalities were indicated for F1a, F2a, and F2b pups. Parental NOEL = 250 ppm (reduced F1 group mean bodyweights). Reproductive NOEL = 1500 ppm. No adverse reproductive effects. Acceptable. (Green and Leung, 4/16/08).

53030-0112 230431, "NOA446510: Preliminary One Generation Reproduction Toxicity Study in Rats, Final Report", (D. Lees, Syngenta Central Toxicology Laboratory, Macclesfield, Cheshire, UK., Report No. CTL/RR0964/TEC/REPT, 20 December 2005). 14 Alpk:AP_rSD (Wistar-derived) rats per group received NOA446510 (96.5%) in the diet at 0 (basal diet), 250, 500, 1500, and 3000 ppm through weaning of F1a litters. During the pre-mating interval (10 weeks), mean dose rates were 23.6, 47.1, 144.9, and 307.9 mg/kg/day for males and 24.2, 49.5, 145.0, and 298.2 mg/kg/day for females at 250, 500, 1500, and 3000 ppm respectively. At 3000 ppm, male group mean bodyweights were lower than controls from pre-mating weeks 3 to 10 (maximum reduction of 7% at week 6). No effect on female bodyweight was noted during gestation. During lactation, female bodyweights were 4% and 7% lower than controls by day 22 at 1500 and 3000 ppm, respectively. Food consumption was increased in males at 1500 and 3000 ppm during pre-mating weeks 1-4. 13, 14, 12, 14, and 9 live litters and 0, 0, 1, 0, and 1 still-born litters were recorded at 0, 250, 500, 1500, and 3000 ppm respectively. Day 22 pup weights were reduced at 500, 1500, and 3000 ppm relative to controls with statistical significance at the high dose level. Mean liver and kidney weights (adjusted for bodyweight) were increased at 1500 and 3000 ppm for males and females compared to controls and seminal vesicle weights were increased for males. Parental and offspring macroscopic findings were unremarkable. Supplemental data. (Green and Leung, 4/1/08).

TERATOLOGY, RAT

**53030-0105, 0104, 0109 230424, 230423, 230428, "NOA446510: Prenatal Developmental Toxicity Study in the Rat, Final Report", (M.E. Moxon, Syngenta Central Toxicology Laboratory, Macclesfield, Cheshire, UK., Report No. RR0963-REG, 14 October 2005). 24 time-mated Alpk:AP_rSD (Wistar-derived) female rats per group received NOA446510 (96.5%) by oral gavage at 0 (0.5% carboxymethylcellulose), 50, 200, and 1000 mg/kg/day on gestation days 5 through 21. There were no treatment-related effects on maternal mortality, bodyweight, food consumption, gross pathology, or reproductive/litter outcomes. Fetal weights, sex ratios, numbers, visceral and skeletal alterations were not effected by treatment. No teratogenicity. Maternal and developmental NOEL = 1000 mg/kg/day. Acceptable. (Green and Leung, 3/27/08).

53030-0104 230423, "NOA446510: Dose Range Finding Study in the Pregnant Rat, Final Report", (M.E. Moxon, Syngenta Central Toxicology Laboratory, Macclesfield, Cheshire, UK, Report Number RR0965-TEC, 19 December 2005). 10 time-mated Alpk:AP_rSD (Wistar-derived) female rats per group received NOA446510 (96.5%) by oral gavage at 0 (0.5% aqueous carboxymethylcellulose), 250, 500, and 1000 mg/kg/day on gestation days 5 through 21. All animals survived to scheduled termination on gestation day 22. The number of pregnant females was 10, 9, 9, and 10 at 0, 250, 500, and 1000 mg/kg/day respectively. One control female had total litter resorption. Maternal clinical signs and bodyweight were not affected by treatment. At 1000 mg/kg/day, mean maternal food consumption was significantly reduced between gestation days 5 and 8 compared to controls (22.3 vs 25.5 g/rat/day, p<0.05). Mean maternal relative liver weights were increased at 1000 mg/kg/day relative to controls (4.1% vs 3.6%). Histopathology revealed focal hepatitis in the liver of 2 dams at 1000 mg/kg/day. Number, growth, and survival of fetuses were not affected by treatment. Teratogenicity was not indicated. No worksheet. (Green and Leung, 3/27/08).

53030-0109 230428, "NOA446510: Rangefinding Prenatal Developmental Toxicity Study in the Rat, Final Report", (B. Altmann, Syngenta Crop Protection, Stein, Switzerland, Syngenta No. T001467-06, 28 December 2001). 8 mated female Wistar rats per group received NOA 446510 (95%) by oral gavage at 0 (0.5% w/w carboxymethylcellulose supplemented with 0.1% w/w Tween 80), 10, 100, and 1000 mg/kg/day on gestation days 6 through 20. Dams were necropsied on gestation day 21. No treatment-related effects on maternal clinical signs, mortality, bodyweight, food consumption, gross pathology, or reproductive parameters. There were no effects on fetal weights, external or visceral alterations, or skeletal development. Maternal and developmental NOEL = 1000 mg/kg/day. No teratogenicity. No worksheet. (Green and Leung, 3/27/08).

TERATOLOGY, RABBIT

**53030-0108 230427, "NOA446510: Prenatal Developmental Toxicity Study in the Rabbit, Final Report", (M.E. Moxon, Syngenta Central Toxicology Laboratory, Macclesfield, Cheshire, UK., Report No. RB0962-REG, 27 October 2005). 24 time-mated, female New Zealand White rabbits per group received NOA446510 (96.5%) by oral gavage at 0 (0.5% w/v aqueous carboxymethylcellulose), 50, 250, and 1000 mg/kg/day on gestation days 5 through 29. Treatment-related effects on maternal mortality, bodyweight, food consumption, gross pathology, and reproductive outcomes and on fetal parameters (weights, sex ratios, numbers, visceral and skeletal alterations) were not indicated. No teratogenicity. Maternal and developmental NOEL = 1000 mg/kg/day. Acceptable. (Green and Leung, 3/27/08).

53030-0106 230425, "NOA446510: Dose Range Finding Study in the Pregnant Rabbit, Final Report", (M.E. Moxon, Syngenta Central Toxicology Laboratory, Macclesfield, Cheshire, UK, Report Number RB0961-TEC, 20 December 2005). 10 time-mated, female New Zealand White rabbits per group received NOA446510 (96.5%) by oral gavage at 0 (0.5% w/v aqueous carboxymethylcellulose), 250, 500, and 1000 mg/kg/day on gestation days 5 through 29. One female at 250 mg/kg/day and another at 1000 mg/kg/day were sacrificed (days 26 and 21 respectively) in distress unrelated to the toxicity of NOA446510. All females were pregnant. There were 10, 9, 10, and 9 females with live litters at scheduled necropsy (gestation day 30) at 0, 250, 500, and 1000 mg/kg/day respectively. Orange-staining was observed on the tray papers of all animals in each treated group throughout the treatment period. Maternal bodyweight and food consumption were significantly reduced at 1000 mg/kg/day compared to controls. Plasma alanine aminotransferase activity was significantly lower for females at 500 and 1000 mg/kg/day compared to controls but with no dose response. Histopathology revealed minimal to slight increased periportal eosinophilia and/or hypertrophy in livers of 2/10 females at 1000 mg/kg/day. The number, growth, and survival of fetuses were not affected by treatment. An increased number of fetuses with fusion of the cartilaginous spinous processes of the sacral and caudal arches were observed in the treated groups. Fusion of the spinous process of the 3rd sacral arch to the spinous process of the 2nd sacral arch was the most common observation. Fetal incidence was significantly higher at 1000 mg/kg/day than for controls. No other changes in skeletal development were indicated. No worksheet. (Green and Leung, 3/26/08).

53030-0107 230426, "NOA446510: Dose Range Finding Study in Non-Pregnant Rabbits, Final Report", (M.E. Moxon, Syngenta Central Toxicology Laboratory, Macclesfield, Cheshire, UK, Report Number RB0934-TEC, 19 December 2005). 2 female New Zealand White rabbits received a daily oral gavage dose of NOA446510 (96.5%) in aqueous 0.5% w/v aqueous carboxymethylcellulose at 250 mg/kg/day for 4 days, followed by 500 mg/kg/day for 4 days, and then by 1000 mg/kg/day for 7 days. Animals were necropsied on day 16. Clinical signs, bodyweight, food consumption, and necropsy findings were not affected by treatment. No worksheet. (Green and Leung, 3/26/08).

GENE MUTATION

** 53030-0116 230435, "NOA446510: Bacterial Mutation Assay in *S. typhmuri* and *E. coli* Final Report Amendment", (R.D. Callander, Syngenta Central Toxicology Laboratory, Macclesfield, Cheshire, UK., Report No. CTL/YV6190/Regulatory/Revision-001, 16 November 2005). Triplicate cultures (5 solvent control cultures) of *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strains WP2P and WP2P *uvrA* were exposed to NOA446510 (96.5%), in the presence and absence of S9 mix, at 0 (DMSO), 100, 200, 500, 1000, 2500 and 5000 ug/plate for 3 days using both the direct plate incorporation method and the preincubation method (treated for 60 minutes at 37° C in Bijoux bottles prior to plate incorporation). The number of revertants per plate was not increased by treatment. In the direct plate incorporation phase, precipitation was noted at 2500 ug/plate and higher in the absence of S9 and at 5000 ug/plate in the presence of activation (*E. coli* strain WP2P also had precipitate at 2500 ug/plate with S9). In the precipitation phase, all strains had a precipitate at 1000 ug/plate and higher in the absence of activation (except *E. coli* strain WP2P *uvrA* with precipitate at 2500 and 5000 ug/plate only); no precipitate was indicated at any level in the presence of S9. Acceptable. (Green and Leung, 4/16/08).

**53030-0117 230436, "NOA446510: L5178Y TK+/- Mouse Lymphoma Mutation Assay, Final Report Amendment", (P. Clay, Syngenta Central Toxicology Laboratory, Macclesfield, Cheshire, UK., Report No. V V0286/Regulatory/Revision-001, 16 November 2005). Duplicate cultures of L5178Y TK^{+/-} mouse lymphoma cells were exposed for 4 hours to NOA446510 (96.5%), in the presence and absence of rat liver S9, at 0 (DMSO), 1, 10, 50, 100, 250, 257, 500, 515, 1030, 2060, or 4119 µg/ml. Reduced relative survival rates for treated cultures vs solvent controls demonstrated adequate dosing levels. Treatment related increases in the mutation frequency were not indicated. Positive controls were functional. Acceptable. (Green and Leung, 4/15/08).

53030-0141 230461, "SYN 500003 (Metabolite of NOA446510): Bacterial Mutation Assay in *S. Typhimurium* and *E. Coli*, Final Report", (R. D. Callander, Syngenta Central Toxicology Laboratory, Macclesfield, Cheshire, UK., Report No. YV7195/Regulatory/Report, 16 February 2006). Triplicate cultures (5 solvent control cultures) of *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strains WP2 and WP2 *uvrA* were exposed to SYN 500003 (metabolite of NOA446510) (99% purity), in the presence and absence of S9 mix, at 0 (DMSO), 100, 200, 500, 1000, 2500 and 5000 µg/plate for 3 days using direct plate incorporation. In an additional assay using the same treatment levels, direct plate incorporation was used in the absence of S9 mix and preincubation (treatment for 60 minutes prior to plate incorporation and 3 day incubation) was used in the presence of activation. The numbers of revertant colonies were not increased by treatment. Reduced background lawn growth and a decrease in the number of revertants were noted for most strains at the high dose level in the absence of activation. Positive controls were functional. Supplemental data. (Green and Leung, 4/16/08).

53030-0142 230462, "SYN545038 (Impurity of Mandipropamid): Bacterial Mutation Assay in *S. Typhimurium* and *E. Coli*, Final Report"; D. Callander, Syngenta Central Toxicology Laboratory, Macclesfield, Cheshire, UK., Report No. YV7241-REG, 22 March 2006). triplicate cultures (5 solvent control cultures) of *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strains WP2 and WP2 *uvrA* were exposed to SYN 545038 (98%), in the presence and absence of S9 mix, at 0 (DMSO), 20, 50, 100, 200, 500, 1000, 2500 or 5000 µg/plate for 3 days at 37° C using direct plate incorporation. A repeat assay was performed. The number of revertants per plate was not increased by treatment in the absence of activation. In the presence of S9 mix, significant, dose-related increases in the numbers of revertants per plate were recorded for strains TA98, TA100, TA1535, TA1537, and WP2 *uvrA*. Precipitate was generally noted at 2500 and 5000 µg/plate, both in the presence and absence of S9, in all strains, and, at 1000 µg/plate, in TA1535 and TA1537 without activation. Positive controls were functional. Supplemental data. (Green and Leung, 4/16/08)

CHROMOSOME EFFECTS

**53030-0118 230438, "NOA446510: *In Vitro* Cytogenetic Assay in Human Lymphocytes, Final Report", (V. Fox, Syngenta Central Toxicology Laboratory, Macclesfield, Cheshire, UK., Report No. CTL/SV1144/Regulatory/Report, 7 November 2002). Duplicate cultures of female whole human blood were exposed, in the presence and absence of rat liver S9, to NOA446510 (96.5%) concentrations of 0 (DMSO), 0 (untreated), 10, 50, 100, 250, 500, 1000, 2000, 3000, and 4119 µg/ml for 3 hours in experiment 1. In experiment 2, duplicate cultures were exposed, in the presence of S9 at 0 (DMSO), 1, 2.5, 5, 10, 25, 50, 100, and 250 µg/ml for 3 hours, and, at the same concentrations for 20 hours in the absence of S9 mix. Cells were harvested 20 hours after the start of treatment (colcemid was added 2 hours prior to harvest). Precipitation of test material in culture medium (slightly cloudy/opaque) was reported at 100 µg/ml and higher. In the first assay, aberrant metaphases were determined at 0, 10, 50, and 100 µg/ml in the absence and presence of S9 mix. In the second assay, aberrant cells were determined at 0, 2.5, 10, and 25 µg/ml in the absence of S9, and at 0, 5, 25, and 50 µg/ml with activation. 100 metaphases per duplicate culture were scored. Treatment levels chosen for chromosome analysis were selected based on the mitotic index (toxicity precluded scoring cells above the levels chosen). No statistically or biologically significant increases in aberrant cells (compared to solvent controls) were indicated. Positive controls were functional. Acceptable. (Green and Leung, 4/15/08).

**53030-0119 230439, "NOA446510: Rat Bone Marrow Micronucleus Test, Final Report", (V. Fox, Syngenta Central Toxicology Laboratory, Macclesfield, Cheshire, UK., Report No. CTL/SR1176/Regulatory/Report, 15 September 2005). 5 male Alpk:AP_rSD (Wistar derived) rats per group received a single oral gavage dose of NOA446510 (96.5%) at 0 (0.5% aqueous methylcellulose) and 2000 mg/kg followed by bone marrow sampling 24 and 48 hours later. No reactions were observed in animals after dosing and evaluation of internal organs revealed no abnormalities. 2000 polychromatic erythrocytes per animal were scored for micronuclei. No increase in micronucleated polychromatic erythrocytes. Positive controls were functional. Acceptable. (Green, 2/11/08).

DNA DAMAGE

**53030-0120 230440, "NOA446510: *In Vivo* Rat Liver Unscheduled DNA Synthesis Assay, Final Report", (P. Clay, Syngenta Central Toxicology Laboratory, Macclesfield, Cheshire, UK., Report No. CTL/SR1193/Regulatory/Report, 31 August 2005). 2 (vehicle and positive control) or 3 male Alpk:AP_rSD (Wistar derived) rats per group received a single oral gavage dose of NOA446510 at 0 (0.5% carboxymethylcellulose) and 2000 mg/kg. Hepatocytes were sampled 2 and 16 hours post-treatment. Viability of the hepatocytes was determined using trypan blue and ranged from 64% to 80%. After attachment, cells were exposed to (methyl-³H) thymidine for 4 hours followed by overnight incubation with unlabelled thymidine. Six cultures were initiated per animal and 3 autoradiographs were prepared. 60 cells per animal were analyzed. There was no increase in net nuclear grain counts. Positive controls were functional. Acceptable. (Green and Leung, 4/16/08).

NEUROTOXICITY

0123, 230443; "NOA 446510: Acute Neurotoxicity Study in Rats" (Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Laboratory Project ID: Report No. CTL/AR7352/Regulatory/Report, Study No. AR7352, Document No. CTL/AR7352/REG/REPT, 10/04/05). 870.62. NOA 446510 (technical) (Batch reference number SEZ2BP007, purity = 96.5%), prepared in 0.5% w/v aqueous carboxymethylcellulose, was administered in a single dose by gavage to 10 Alpk:AP_rSD (Wistar-derived) rats per sex per dose at dose levels of 0 (vehicle only), 200, 600, and 2000 mg/kg. No treatment-related mortalities occurred. No treatment-related clinical signs were observed. No effects on body weight were observed. A statistically significant ($p < 0.01$) and dose-related decrease in mean hindlimb grip strength was observed at all 3 dose levels. FOB assessments revealed no other treatment-related effects on days 1, 8, and 15. Motor activity assessments revealed no treatment-related effects on days 1, 8, and 15. Macroscopic and microscopic examinations revealed no treatment-related abnormalities. **No adverse effects.** NOEL (M) = 2000 mg/kg (based on no effects at the highest dose tested); NOEL (F) not determined (based on a dose-related decrease in mean hindlimb grip strength at the lowest dose tested). **Acceptable.** (Corlett and Leung, 12/06/07)

0121, 230441; "NOA 446510: Subchronic Neurotoxicity Study in Rats" (Pinto, P.J., Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Laboratory Project ID: Report Number CTL/PR1294/Regulatory/Report, Syngenta Number T008126-03, 11/15/05). 870.6200. NOA 446510 (Technical) (Batch reference number SEZ2BP007, purity = 96.5%) was admixed to the diet and fed to 12 Alpk:AP_rSD (Wistar-derived) rats per sex per dose at dose levels of 0, 100, 500, or 2500 ppm (0, 7.4, 37.3, and 192.5 mg/kg/day, respectively for males and 0, 8.4, 41, and 206.7 mg/kg/day, respectively for females) for at least 90 consecutive days. No animals died during the study. No treatment-related clinical signs were observed. A treatment-related decrease in adjusted mean body weight (determined by analysis of covariance) was observed in males at 2500 ppm. FOB and motor activity assessments revealed no treatment-related effects. A treatment-related increase in mean liver weight adjusted to body weight (determined by analysis of covariance) was observed in both sexes (non-perfused animals) at 2500 ppm. Neuropathological examination on the central and peripheral nervous systems revealed no treatment-related effects. No evidence of neurotoxicity was indicated. **No adverse effects.** NOEL (M) = 37.3 mg/kg/day (500 ppm) and NOEL (F) = 41 mg/kg/day (500 ppm) based on an increase in liver weight. **Acceptable.** (Corlett and Leung, 02/04/08).

METABOLISM

**53030-0124 230444, "NOA446510: Tissue Depletion Following a Single Oral Dose (3 mg/kg and 300 mg/kg) in the Rat, Final Report", (K. Roberts, Syngenta Central Toxicology Laboratory, Macclesfield, Cheshire, UK., Study No. CTL/UR0761/Regulatory/Report, 20 October 2005). 9 or 15 Alpk:AP_rSD (Wistar-derived) rats per sex per group received a single oral gavage dose of [Methoxyphenyl-U-¹⁴C] NOA446510 at 3 and 300 mg/kg. In phase 1, serial blood samples were taken (tail veins) from 3 rats per sex per group at 2, 4.5, 6.5, 8-8.5, 9.5-10, 13, 18, 24, 34, 48, 72, and 96 hours after dosing at 3 mg/kg (group 1) and 300 mg/kg (group 2). Results were used to select termination times for phase 2 animals. In phase 2, three rats per sex per group were terminated 8, 24, 48, 72, and 96 hours after treatment at 3 mg/kg (group 3) and 300 mg/kg (group 4). Blood samples (separated into plasma and blood), adrenals, brain, heart, kidneys, liver, lungs, ovaries, pancreas, spleen, thymus, thyroid, testes, uterus, bone (femur), fat (abdominal), and muscle from each animal were analyzed (LSC) for radioactivity at each time point. In phase 1, group mean peak blood radioactivity concentration times (T_{max}) were 8.5 hours for males and 4.5 hours for females and half-lives of elimination of radioactivity ($t_{1/2}$) were 18.4 hours (males) and 20.2 hours (females) after dosing at 3 mg/kg. At 300 mg/kg, group mean T_{max} values were 24 hours (males) and 10 hours (females), while $t_{1/2}$ values were 32.7 hours for males and 24.8 hours (females). In phase 2, at both dose levels, tissue concentrations of radioactivity were slightly lower in females compared to males. Liver and kidney tissue residues were the only measurements consistently higher than plasma concentrations (plasma concentrations were 0.13 μ g equivalents/g (males) and 0.10 μ g equivalents/g (females) at 3 mg/kg and 5.12 μ g equivalents/g (males) and 2.65 μ g equivalents/g (females) at 300 mg/kg) for both sexes at both dose levels. All tissue concentrations declined to values that were low or below the limit of detection by 96 hours post-treatment. Highest group mean concentrations of radioactivity were in liver at 8 hours: 1.25 μ g equivalents/g (2.04% of dose) (males) and 0.64 μ g equivalents/g (0.94% of dose) (females) at 3 mg/kg, and 46.4 μ g equivalents/g (0.77% of dose) (males) and 27.1 μ g equivalents/g (0.39% of dose) (females) at 300 mg/kg. Values for kidneys at 8 hours were 0.26 μ g equivalents/g (0.08% of dose) for males and 0.25 μ g equivalents/g (0.08% of dose) for females at 3 mg/kg, and 10.43 μ g equivalents/g (0.04% of dose) for males and 6.9 μ g equivalents/g (0.02% of dose) for females at 300 mg/kg. Group mean $t_{1/2}$ values for liver at 3 mg/kg were: 23.6 and 23.1 hours for males and females respectively, and for kidney, were 22.2 and 21.5 hours for males and females respectively. At 300 mg/kg, group mean $t_{1/2}$ values for liver were 19.1 and 17.7 hours for males and females respectively and, for kidneys, 19.5 hours (males) and 15.6 hours (females). Group mean $t_{1/2}$ values for other tissues generally ranged from 18 to 24 hours (except for thymus (31.5 hours) and testes (30.0 hours) in males at 300 mg/kg). Acceptable. (Green and Leung, 4/15/08).

**53030-0126 230446, "NOA446510: Absorption, Distribution, and Excretion in the Rat, Final Report", (R.C. Silcock and A. Duerden, Syngenta Central Toxicology Laboratory, Macclesfield, Cheshire, UK., Report No. CTL/UR0719/REG/REPT, 9 November 2005). 1 or 4 Alpk:AP_rSD (Wistar-derived) rats per sex per group received a single oral gavage dose of [Chlorophenyl-U-¹⁴C] NOA446510 or [Methoxyphenyl-U-¹⁴C] NOA446510 at 3 and 300 mg/kg. Following dosing, exhaled carbon dioxide from 1 per sex per group (groups 2, 6, and 7) was collected in traps containing 2N sodium hydroxide solution and exhaled metabolites were collected in charcoal traps at 8 or 10 (females), 24, 36, and 48 hours. Residues in expired carbon dioxide and volatile metabolites were near or below the limit of detection at all time points for both [chlorophenyl-U-¹⁴C] NOA446510 and [methoxyphenyl-U-¹⁴C] NOA446510 radiolabels. At 3 mg/kg after 48 hours, the total radioactivity in expired air amounted to less than 0.1% of dose in males and females for [chlorophenyl-U-¹⁴C] NOA446510 and less than 0.2% of dose for both sexes for [methoxyphenyl-U-¹⁴C] NOA446510. No radioactivity (metabolites) was recovered in the charcoal traps. 48 hours after 300 mg/kg of [methoxyphenyl-U-¹⁴C] NOA446510, radioactivity in expired air amounted to less than 0.2% of dose in both sexes and no radioactivity was recovered in the charcoal traps. Following dosing of the excretion and tissue distribution phase animals (4 rats per sex per group in groups 3, 4, 8, and 9), urine was collected at 6 and 10 hours and urine and feces at 24, 48, 72, 96, 120, 144, and 168 hours post-treatment. The mean total percentages of radioactivity excreted in urine and feces over 168 hours were similar for the [chlorophenyl-U-¹⁴C] NOA446510 and

[methoxyphenyl-U-¹⁴C] NOA446510 radiolabels. The major route of excretion was feces at both dose levels, while a greater proportion of administered dose was excreted in urine at the low dose vs 300 mg/kg and for females compared to males. At 300 mg/kg, fecal excretion accounted for mean totals of 87%-91% in males and 81%-84% in females, while urinary excretion accounted for mean totals of 2.2%-3.3% for males and 6.4%-11.6% for females. At 3 mg/kg, mean totals for fecal excretion were 76%-81% in males and 42%-55% in females, and urinary excretion accounted for mean totals of 14%-15% in males and 29%-47% in females. Tissue distribution of radioactivity was similar for both radiolabels and both sexes seven days after treatment. At 3 mg/kg, radioactivity in tissues accounted for 0.06%-0.17% of dose in total and radioactivity remaining in the carcass was 0.08%-0.19% of dose. Highest radioactive concentrations were in liver (0.033-0.085 μg equivalents/g (0.05%-0.16% of dose)), kidney (0.007-0.019 μg equivalents/g (<0.01% of dose)), and thyroid (<0.010-0.030 μg equivalents/g (<0.01% of dose)). Concentrations in all other tissues were below 0.010 μg equivalents/g. At 300 mg/kg/day, radioactivity in tissues was 0.02%-0.04% of dose in total and radioactivity in residual carcass was 0.01%-0.11% of dose. Highest radioactive concentrations were also in liver (0.81-1.57 μg equivalents/g (0.01%-0.03% of dose)), kidney (0.12-0.35 μg equivalents/g (<0.01% of dose)), and thyroid (<0.17-1.20 μg equivalents/g (<0.01% of dose)). Radioactivity in whole blood and plasma was <0.08-0.24 μg equivalents/g and <0.01-0.04 μg equivalents/g respectively. Concentrations in all other tissues were below 0.10 μg equivalents/g. In the phase using bile duct cannulated rats (4 rats per sex per group in groups 10 and 11), urine was collected at 10 (females) or 12, 24, and 48 hours after dosing, feces at 24 and 48 hours, and bile at 1, 2, 3, 4, 5, 6, 7, 8, 10 (females) or 12, 24, 36, and 48 hours post-dosing. In bile duct cannulated rats that received [methoxyphenyl-U-¹⁴C] NOA446510 at 3 mg/kg, the majority of administered dose was eliminated in bile (73% for males and 55% for females) after 48 hours; fecal excretion was 14% and 22% for males and females respectively; and urinary excretion was 1.4% for males and 9.5% for females. At 300 mg/kg, biliary excretion was 28% and 22% for males and females respectively; feces contained 39% (males) and 26% (females); and urine accounted for 0.8% (males) and 19% (females) of dose after 48 hours. Acceptable. (Green and Leung, 4/15/08).

**53030-0127 230447, "NOA446510: Tissue Accumulation and Depletion Following Multiple Oral Dosing (3 mg/kg) in the Rat, Final Report", (K. Roberts, Syngenta Central Toxicology Laboratory, Macclesfield, Cheshire, UK., Study No. CTL/UR0786/REG/REPT, 12 October 2005. 3 male Alpk:AP_rSD (Wistar-derived) rats per group received [Methoxyphenyl-U-¹⁴C] NOA446510 at 3 mg/kg/day for up to 14 days. Groups of 3 males were terminated 24 hours after 3, 7, 10, and 14 consecutive daily doses and 1, 4, 7, 14, 21, 28, and 49 days after the last of 14 consecutive daily doses. Adrenals, brain, heart, kidneys, liver, lungs, pancreas, spleen, thymus, thyroid, testes, along with samples of blood, plasma, bone (femur), fat (abdominal), and muscle were analyzed for radioactivity (LSC). Urine, feces, and cage wash were collected from 3 males 24 hours after the first dose and 24 hours after the 14th consecutive dose and analyzed for radioactivity (LSC). Tissue concentrations of radioactivity reached a steady state within 4 days of the initial dose and subsequently declined rapidly after the cessation of dosing. After 14 consecutive daily doses mean tissue [¹⁴C] concentrations were highest in liver (0.727 μg equivalents/g) and kidneys (0.234 μg equivalents/g). The elimination from liver was biphasic with terminal elimination half life calculated as 4.2 days and distribution half life calculated as 2.3 days. In kidneys, the elimination half life was 8.7 days. Bone elimination half life was 12.8 days. All other tissue concentrations at steady state were generally low (0.1 μg equivalents/g or less) with radioactivity declining below the limit of detection a few days after the last dose. The majority of radioactivity was excreted in feces (79% of dose after 1 dose and 66% after 14 consecutive doses). Urine contained 2.6% of dose after 1 dose and 7% after 14 consecutive doses. Acceptable. (Green and Leung, 4/15/08).

53030-0125 230445. This study evaluated the metabolites/components in pooled samples of feces, urine, and bile from male and female Alpk:AP_rSD (Wistar-derived) rats from two previous Syngenta studies, Report No. CTL/UR0719/REG/REPT (record 230446) and Report No. CTL/UR0786/REG/REPT (record 230447). In Report No. CTL/UR0719/REG/REPT (record 230446), pooled samples of urine and feces from 4 rats per sex per group (Groups 3, 8, and 9 listed in table below) that received a single oral gavage dose of [Chlorophenyl-U-¹⁴C] NOA446510

at 300 mg/kg and [methoxyphenyl-U-¹⁴C] NOA446510 at 3 and 300 mg/kg were evaluated for metabolites/components. Additionally, urine, feces, and bile from 4 bile duct cannulated rats per sex per group (Groups 10 and 11) that received a single oral gavage dose of [methoxyphenyl-U-¹⁴C] NOA446510 at 3 and 300 mg/kg were evaluated. In Report No. CTL/UR0786/REG/REPT (record 230447), pooled samples of urine and feces from 3 males were evaluated for metabolites/components 24 hours after a single oral gavage dose with 3 mg/kg of [methoxyphenyl-U-¹⁴C] NOA446510 and 24 hours after 14 consecutive doses at 3 mg/kg. All major metabolites/components, representing greater than 5% of administered dose were identified (high performance liquid chromatography (HPLC) and mass spectrometry (MS)). The proposed metabolic pathway was described: loss of one or both of the propargyl groups followed by glucuronidation and O-demethylation (a schematic was included). Differences in metabolism of the two radiolabeled species were not indicated. Metabolic profiles of excreta following administration of both the chlorophenyl and methoxyphenyl radiolabeled forms at the high dose level (300 mg/kg) were qualitatively and quantitatively similar. Single Dose of 3 mg/kg [Methoxyphenyl-U-¹⁴C] NOA446510 Females excreted 46% of the dose in urine and 41% in feces during 96 hours. The major urinary metabolite (40% of dose) was NOA458422 glucuronide (the O-glucuronide of NOA458422 (2-(4-chloro-phenyl)-N-[2-(4-hydroxy-3-methoxy-phenyl)-ethyl]-2-prop-2-ynoxy-acetamide)). In feces, NOA446510 was 12% of dose and NOA458422 was 19%. Males excreted 14% of dose in urine and 72.3% in feces during 96 hours. The major urinary metabolite (10% of dose) was SYN534133 (the glucuronide of CGA 380775 (2-(4-chloro-phenyl)-2-hydroxy-N-[2-(4-hydroxy-3-methoxy-phenyl)-ethyl]acetamide)). In feces NOA458422, parent, and NOA458422 glucuronide accounted for 29.2%, 21.3%, and 12.9% of dose respectively. 14 Consecutive Daily Doses in Males at 3 mg/kg [Methoxyphenyl-U-¹⁴C] NOA446510 Component profiles of excreta were similar between samples taken 24 hours after the first and 14 doses and consistent with results in the single dose study above. Single Dose of 300 mg/kg [Chlorophenyl-U-¹⁴C] NOA446510 Females excreted 6% of dose in urine and 81% of dose in feces during 96 hours. NOA458422 glucuronide was the major urinary metabolite (3.7% of dose). NOA446510 accounted for 75% of dose in feces of females. Males excreted 2% of dose in urine and 86% of dose in feces during 96 hours. SYN534133, at 1% of dose, was the major urinary metabolite. NOA446510 accounted for 79% of dose in feces. Single Dose of 300 mg/kg [Methoxyphenyl-U-¹⁴C] NOA446510 Females excreted 11% of dose in urine and 82% of dose in feces during 96 hours. NOA458422 glucuronide (7% of dose) and NOA446510 (71% of dose) were the major components in urine and feces respectively. Males had 3% of dose in urine and 90% of dose in feces during 96 hours. SYN534133, accounting for 2% of dose, and NOA446510 (73% of dose) were the major components in urine and feces respectively. Single Dose of 3 mg/kg [Methoxyphenyl-U-¹⁴C] NOA446510 with Bile Duct Cannulated Rats During 48 hours, females excreted 15% of dose in urine, 46% of dose in bile, and 22% of dose in feces. The major component in urine and bile was NOA458422 glucuronide at 10% and 41% of dose respectively. NOA446510 was the major component in feces (22.3% of dose). Males excreted 1%, 73%, and 15% of dose in urine, bile, and feces respectively during 48 hours. NOA458422 glucuronide was the major component in urine (0.7% of dose) and bile (62.2% of dose). NOA446510 accounted for 13% of dose in feces. Single Dose of 300 mg/kg [Methoxyphenyl-U-¹⁴C] NOA446510 with Bile Duct Cannulated Rats 28%, 12%, and 37% of administered radioactivity was excreted by females in urine, bile, and feces respectively during 48 hours. NOA458422 glucuronide was the major component in urine (25% of dose) and bile (10% of dose). NOA446510 accounted for 37% of dose in feces. Males excreted 1% of dose in urine, 28% in bile, and 39% in feces during 48 hours. NOA458422 glucuronide was the major component in urine (0.5% of dose) and bile (22.5% of dose). NOA446510 was 38.6% of dose in feces of males. (Green and Leung, 4/15/08).

53030-0143 230463, "NOA446510: Programme to Investigate Dose NOA446510 Versus Oral Absorption/Systemic Exposure Relationship in Mice", (E. Booth and K. Roberts, Syngenta Central Toxicology Laboratory, Macclesfield, Cheshire, UK., Report No. CTL/024843/TEC/REPT, 17 March 2006). In an oral gavage study, 27 C57BL/10J_r/Alpk mice per sex per group received a single oral dose of [Methoxyphenyl-U-¹⁴C] NOA446510 at 10, 50, and 500 mg/kg. In a preliminary dietary study, 55 C57BL/10J_r/Alpk mice per sex received [Methoxyphenyl-U-¹⁴C] NOA446510 in the diet at 800 ppm for 2 days. In the main dietary study, 28 C57BL/10J_r/Alpk mice per sex per

group received [Methoxyphenyl-U-¹⁴C] NOA446510 in the diet at 300, 800, 2000, and 5000 ppm for 7 days. In an intravenous study, 5 C57BL/10J_{+/Alpk} mice per sex received a single intravenous dose of [Methoxyphenyl-U-¹⁴C] NOA446510 at 10 mg/kg. In the single dose oral gavage study, the majority of radioactivity was excreted within the first 24 hours after dosing with no sex differences in either route or rate. At 10 and 50 mg/kg, males excreted 29% of dose in urine at both levels and 32% (10 mg/kg) and 27% (50 mg/kg) in feces during 48 hours after treatment. Females excreted 29% and 47% of dose in urine and 21% and 24% in feces at 10 and 50 mg/kg respectively over the same time period. At 500 mg/kg, feces were the main route of excretion, accounting for 54% of dose in males and 40% in females. Radioactivity in urine represented 16 % of dose in males and 11% in females. No sex differences and no dose level differences in the pharmacokinetics of plasma were indicated. At every time point and dose level, the concentration of radioactivity measured in whole blood was ~half that measured in plasma. At 10 and 50 mg/kg, absorption was rapid with maximum plasma concentrations (C_{max}) reached within 30 minutes of dosing (2 μ g/ml (males) and 3 μ g/ml (females) and 11 μ g/ml (males) and 16 μ g/ml (females) at 10 and 50 mg/kg respectively). The area under the plasma concentration vs time curve (AUC, h. μ g equivalents/ml) at 50 mg/kg was ~5 times that at 10 mg/kg (88 vs 17 for males and 76 vs 17 for females), indicating a linear absorption increase. The absorption phase was slower at 500 mg/kg with plasma C_{max} of 40 μ g/ml (males) and 39 μ g/ml (females) reached 6 hours (males) and 2 hours (females) after treatment. Additionally, at 500 mg/kg, AUC values were 6 fold (543 h. μ g equivalents/ml) and 7 fold (535 h. μ g equivalents/ml) in males and females respectively compared with the expected 10 fold differential vs 50 mg/kg. In urine, five principal metabolites were measured accounting for more than 90% of radioactivity in all samples. Metabolite 4 (NOA458422 glucuronide (the O-glucuronide of NOA458422 (2-(4-chloro-phenyl)-N-[2-(4-hydroxy-3-methoxy-phenyl)-ethyl]-2-prop-2-ynloxy-acetamide)) was the main component and metabolite 2 (only a diagram was provided) the second, at all 3 dose levels. Unchanged NOA446510 was not present in urine. At 10 mg/kg, the metabolic profile of the 0-24 hour feces sample was similar to the urine profile and a small amount of NOA446510 was detected in males but not females. At 50 and 500 mg/kg, the major component in feces was unchanged NOA446510 in both sexes. In plasma, metabolite 4 was the major component in both sexes at all dose levels; metabolite 2 was a very minor component at 10 and 50 mg/kg; and a small amount of unchanged NOA446510 was detected at 500 mg/kg. In the 2 day dietary study at 800 ppm, C_{max} in whole blood was reached at 38.5 hours (males) and 41.0 hours (females) after the start of dosing. In the 7 day dietary study, as with the oral gavage study, radioactivity was associated with the plasma compartment of blood and no sex differences were indicated and radioactivity was proportional to dose level (although specific plasma radioactivity concentration data were limited by lack of achieved dose calculations). Urinary metabolite profiles were qualitatively and quantitatively similar to those for oral gavage animals and were indicated to be independent of sex, dose level, and number of doses. Metabolite 4 was the major urinary component and no unchanged NOA446510 was detected in any samples. Fecal samples had unchanged NOA446510 in all samples. Metabolites 2 and 4 were present in all plasma samples and unchanged NOA446510 was not detected. In the single dose intravenous study (10 mg/kg), the majority of radiolabel was also excreted within 24 hours of dosing. Urine contained 58% (males) and 72% (females) of dose during 24 hours and feces had 25% (males) and 40% (females). Urinary metabolite profiles observed from the 0-24 hour and 24-48 hour post treatment collections were the same as those observed following oral gavage dosing with no qualitative sex differences. Loss of the propargyl groups and glucuronidation was suggested as the principal route of biotransformation. Supplemental data. (Green and Leung, 4/16/08).

53030-0144 230464, "NOA446510: Acute High Dose Study in Rats, Final Report", (P.J. Pinto, Syngenta Central Toxicology Laboratory, Macclesfield, Cheshire, UK., Report No. AR7329-TEC, 16 March 2006). The study was performed to help characterize the mechanistic steps that contribute to the liver as the target organ of NOA446510 in rats. 5 Alpk:AP_rSD (Wistar-derived) rats per sex per group received a single oral gavage dose of NOA446510 (96.5%) at 0 (0.5% aqueous carboxymethylcellulose) or 5000 mg/kg followed by sacrifice 6, 12, 24, or 48 hours later. No signs of clinical toxicity and no treatment-related effects on bodyweight were recorded. Group mean relative liver weights were increased in both sexes at 12, 24, and 48 hours post-treatment

for animals that received 5000 mg/kg vs controls. Gross pathology was unremarkable. Liver histology revealed increased periportal eosinophilia in 4/5 treated males at 12 hours and in 3/5 males at 48 hours. 3/5 females had increased hepatocellular periportal eosinophilia at 48 hours. A minimal increase in mitosis in the liver was recorded for 3/5 males and 3/5 females at 24 hours and for 5/5 males and 1/5 females at 48 hours after 5000 mg/kg. Hepatocellular degeneration or necrosis was not indicated. Supplemental data. (Green, 3/6/08).

53030-0145 230465, "NOA446510: Acute High Dose Study in the Mouse, Final Report", (P.J. Pinto, Syngenta Central Toxicology Laboratory, Macclesfield, Cheshire, UK., Report No. AM7330-TEC, 16 March 2006). The study was performed to help determine the mechanistic steps that contribute to the liver as the target organ of NOA446510 in mice. Five C57B1/10J,CD-1/Alpk mice per sex per group received a single oral gavage dose of NOA446510 (96.5%) at 0 (CMC) or 5000 mg/kg followed by sacrifice 6, 12, 24, or 48 hours later. No treatment-related clinical signs were reported. A slight (statistically significant) decrease in bodyweights (3% vs control values) for males that received 5000 mg/kg at the 12 hour sacrifice time was recorded. No treatment-related macroscopic or microscopic findings were indicated for the liver. These data are supplemental to NOA446510. (Green and Leung, 4/16/08).

53030-0146 230466, "NOA446510: Preliminary Metabolism and Bioavailability in the Dog, Final Report", (A. Wake, Syngenta Central Toxicology Laboratory, Macclesfield, Cheshire, UK., Report No. CTL/UD0763/TEC/REPT, 14 March 2006). In phase 1, one Alderley Park Beagle dog per sex per group received a single oral (gelatin capsule) dose of [Chlorophenyl-U-¹⁴C] NOA446510 at 100 and 800 mg/kg on days 1 and 15. The same animals also received unlabeled NOA446510 on days 5 through 14 at 100 and 800 mg/kg/day. In phase 2, one dog per sex per group received a single intravenous dose of [¹⁴C] NOA446510 at 3 mg/kg on day 1 and a subsequent single radiolabeled oral dose at 3 mg/kg on day 15. Following each radiolabeled dose, animals were placed into metabolism cages and urine and feces were collected (at room temperature) 6, 12, 24, 36, 48, and 72 hours after dosing. In phase 1, blood samples (5 ml) were collected at 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, and 72 hours on day 1 after dosing, and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 hours on day 15. In phase 2, blood sampling times on day 1 were 2, 5, 10, 20, and 30 minutes and 1, 2, 3, 4, 6, 12, and 24 hours post-treatment, and, on day 15, blood was sampled 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 hours after dosing. Phase 1 In phase 1, after a single oral radiolabeled dose (gelatin capsule) at 100 mg/kg, 7% of dose for the male and 22% for the female respectively was excreted in urine over 72 hours. Feces contained 95% (male) and 63% (female) of dose over 72 hours. Maximum plasma concentrations (C_{max}), 6.7 and 4.6 μg equivalents/g, were reached 4 and 8 hours after dosing (T_{max}) for the male and female respectively. The area under the plasma concentration vs time exposure curve values (AUC_{0-24} (h. $\mu\text{g}/\text{g}$)) were 67 and 51 for the male and female respectively. Unchanged NOA446510 represented 73% (male) and 54% (female) of dose in feces (three other minor metabolites were found in feces). Six hour urine samples contained 5 major metabolites (no unchanged NOA446510 was found). Male and female pooled plasma contained unchanged NOA446510 and 5 other metabolites. See study for diagrams, mass spectra, HPLC chromatograms, etc. of metabolites/components. After a single dose at 800 mg/kg, 4% of radioactive dose was excreted in urine of both sexes and 71% (male) and 18% (female) of dose was found in feces over 72 hours. Plasma C_{max} concentrations were 25.0 and 17.5 μg equivalents/g reached at T_{max} times of 6 and 10 hours after treatment for the male and female respectively. The resulting total exposure/time (AUC_{0-24}) values were 98 h. $\mu\text{g}/\text{g}$ (male) and 152 h. $\mu\text{g}/\text{g}$ (female). In feces, the majority of recovered dose was unchanged NOA446510, 67% (male) and 12% (female). 5 major metabolites (4 were the same as at the 100 mg/kg single dose) were found in the 6 hour urine samples (no unchanged NOA446510). Unchanged NOA446510 and 3 of the metabolites found in the 100 mg/kg single dose samples were identified in the 0-48 hour male and female plasma pools. Following the repeat [¹⁴C] NOA446510 dose at 100 mg/kg, 6% and 5% of dose was excreted in urine by the male and female dog respectively with 77% (male) and 79% (female) in feces over 72 hours. C_{max} values of 6.0 and 4.3 μg equivalents/g were reached 4 and 10 hours after dosing (T_{max}) in the male and female respectively, resulting in (AUC_{0-24}) values of 72 and 48 h. $\mu\text{g}/\text{g}$ respectively. Unchanged NOA446510 was identified as the major component in feces, 59% (males) and 70% females (3 minor metabolites were also found in feces). 6 hour urine samples contained the same 5

metabolites as the single dose 100 mg/kg plus 2 others and no unchanged NOA446510. The male and female plasma pool contained unchanged NOA446510, the same 3 metabolites found in the single dose 800 mg/kg samples, and an unidentified minor species. After the repeat oral 800 mg/kg radiolabeled dose, 3% (male) and 4% (female) of dose was found in urine, and feces contained 91% (male) and 94% (female) of dose during 72 hours. C_{max} concentrations were 49.7 and 28.6 μg equivalents/g at 6 hours after treatment (T_{max} for both sexes). AUC_{0-24} values for total exposure/time were 379 h. μg /g (male) and 410 h. μg /g (female). Unchanged NOA446510 accounted for 52% (male) and 93% (female) of dose in feces. Six hour urine samples contained the same 5 metabolites as the 800 mg/kg single dose group. 0-48 hour plasma samples contained NOA446510 and the same 3 metabolites as in the single dose 800 mg/kg samples (a fourth metabolite was also identified in female plasma). Phase 2 The male dog excreted 24% of dose and the female 31% in urine during 72 hours after the single intravenous radiolabeled 3 mg/kg dose with 45% (male) and 47% (female) of dose in feces. Major urinary metabolites were identified as the same 5 found in the single dose oral 100 mg/kg group samples in phase 1, plus one other. In male 0-24 hour plasma pools, unchanged NOA446510 and 5 of the metabolites identified in the phase one, 100 mg/kg single oral dose samples, plus one other, were detected. After the single radiolabeled oral dose (gelatin capsule) at 3 mg/kg on day 15, urine contained 14% (male) and 21% (female) of dose, and feces contained, 72% (male) and 66% (female) of dose during 72 hours. Major urinary metabolites for each sex were identified as the same 5 detected in the phase 1, single oral 100 mg/kg dose samples (female samples also contained a 6th species). In male and female 0-24 hour plasma pools, 2 of the 3 metabolites found in the phase 1 single oral dose 800 mg/kg samples plus one other were identified (other species were detected but at levels too low to identify). The proposed metabolic pathway was presented: loss of one or both propargyl groups followed by conjugation with glucuronic or sulphuric acid and O-demethylation with no cleavage of the molecule. Supplemental data. (Green and Leung, 4/15/08).

53030-0147 230467, "NOA446510: Investigative Metabolism in the Rat, Final Report", (K. Roberts, Syngenta Central Toxicology Laboratory, Macclesfield, Cheshire, UK., Report No. CTL/UR0717/TEC, 17 March 2006). In phase 1, three Alpk:AP_rSD (Wistar-derived) rats per sex per group (groups 1, 2, and 3) received unlabeled NOA446510 (96.5%) in the diet at 100, 500, and 5000 ppm for 11 consecutive days followed by radiolabeled diet at the corresponding levels on day 12. Additionally, in phase 1, three rats per sex per group (groups 4, 5, and 6) received unlabeled NOA446510 by oral gavage for 11 consecutive days at 10, 50, and 500 mg/kg/day followed by a single oral dose of [Methoxyphenyl-U-¹⁴C] NOA446510 on day 12 at the same levels. In phase 2, six rats per sex per group (groups 7, 8, and 9) received unlabeled NOA446510 in the diet for 11 consecutive days followed [sup>14C] NOA446510 containing diets on the 12th day. In phase 1, urine and feces for groups 1 through 6 were collected (frozen upon excretion, by collection over solid carbon dioxide) separately at 24 hours after the radiolabeled dose and every 24 hours thereafter until termination at 168 hours post dose. Feces samples were pooled together for the 0 to 168 hour period. At collection times, each cage was rinsed with water (30 ml) and washings were collected separately. A terminal blood sample was collected from phase 1 animals. In phase 2, serial blood samples (0.5 ml) were collected (tail veins) from 3 rats per sex per group beginning 3 hours after the start of treatment with radiolabeled diet and continuing every 3 hours thereafter until termination (24 or 48 hours after treatment). Phase 1 Urinary excretion of radiolabel administered in the diet was greater in females compared to males with little or no difference/change as dose increased (suggesting absorption was not saturable). In groups 1, 2 and 3, males excreted a range of 5% to 8% of dose in urine compared to a range for females of 32% to 37% at 100, 500, and 5000 ppm during 168 hours after radiolabeled dose. In groups 4, 5, and 6, there was also a marked sex difference in percentage of administered radiolabel excreted in urine. However, as the gavage dose level increased, the amount of urinary excretion decreased for both sexes, indicating absorption may be saturable by this route. Males excreted 8% of the 10 mg/kg dose and 2% of the 500 mg/kg dose while females excreted 36% of radioactivity at 10 mg/kg and 9% of dose at 500 mg/kg during 168 hours. The majority of radioactivity was excreted in feces, regardless of route (93% to 97% for males and 61% to 65% for females via diet; and 93% to 97% for males and 63% to 92% for females via oral gavage). Limited amounts of radioactivity remained in plasma and carcasses of phase 1 animals at

termination (in many cases, radioactivity was below the limit of detection in both plasma and carcasses). Metabolites were identified (high performance liquid chromatography-mass spectrometry (HPLC-MS)) in urine and plasma. The urinary metabolite profile differed for males and females mainly due to the major metabolite found in female urine NOA458422 glucuronide (formed by glucuronidation of NOA446510 after loss of one of the propargyl groups) which was present in only negligible amounts (if at all) in male samples (may indicate a difference in the route and mechanism of clearance). All other male and female urinary metabolites were present in similar proportions. Plasma profiles were the same for males and females. The majority of metabolites were glucuronides. See study for proposed structures, diagrams, descriptions, mass spectra, HPLC chromatograms, etc. of metabolites/components. SYN 534133 (a glucuronide of NOA446510 after loss of both propargyl groups), present at similar concentrations in urine of both males and females, was the major metabolite in male samples. NOA458422 glucuronide was the major metabolite in both male and female plasma. Phase 2 Area under the plasma concentration vs time exposure curve values ($AUC_{0-48}(\text{ug.h.g}^{-1})$) increased linearly with dietary dose level similarly for both sexes over 48 hours (9.5, 31.9, and 344.0 ug.h.g^{-1} for males and 8.0, 34.9, and 328.9 ug.h.g^{-1} for females at 100, 500, and 5000 ppm respectively). Supplemental data. (Green and Leung, 4/15/08).

SUBCHRONIC STUDIES

Rat 4-Week Dietary Toxicity Study

0095, 230414; "NOA 446510: 28 Day Dietary Range Finding Study in Rats" (Pinto, P.J., Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Laboratory Project ID: Study Number CTL/KR1472/Technical Toxicology/Report Syngenta Number T005177-01, 12/21/05). 870.3050. NOA 446510 (Technical) (Batch reference number KI-6380/6, purity = 98.5%) was admixed to the diet and fed to 5 Alpk:AP_iSD (Wistar-derived) rats per sex per dose at dose levels of 0, 1000, 3000, 10000 or 16000 ppm (0, 135.0, 417.6, 623.8, and 603.6 mg/kg/day, respectively for males and 0, 120.6, 380.6, 783.9, and 1409.9 mg/kg/day, respectively for females) for 28 consecutive days. Animals dosed with 10000 and 16000 ppm were sacrificed on days 2-4 because of marked body weight loss. No treatment-related clinical signs were observed. Treatment-related decreases in mean hematocrit and hemoglobin levels were observed in both sexes at 3000 ppm. A treatment-related increase in the mean γ -glutamyl transferase level in females at 3000 ppm and treatment-related decreases in mean creatinine, albumin, total protein, and total bilirubin in males at 3000 ppm were observed. Urinalysis revealed no effects of toxicological significance. A treatment-related increase in liver weight adjusted to body weight (determined by analysis of covariance) was observed in both sexes at 1000 and 3000 ppm. Treatment-related increases in cytochrome b5, 7-ethoxyresorufin, and glutathione-S-transferase enzyme activities in both sexes at 3000 ppm and a treatment-related increase in 7-ethoxyresorufin in males at 1000 ppm were observed. Microscopic examination revealed a treatment-related increase in eosinophilia and hypertrophy of the periportal hepatocytes in both sexes at 3000 ppm. **No adverse effects.** NOEL not determined (treatment-related increased mean liver weight at 1000 ppm in both sexes). **Acceptable.** (Corlett, 01/17/08)

Rat Subchronic Dietary Toxicity Study

0097, 230416; "NOA 446510: 90-Day Oral Toxicity Study in Rats" (Pinto, P.J., Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Laboratory Project ID: Report Number PR1263-REG-R1, Syngenta Number T004583-02, 11/15/05). 870.3100. NOA 446510 (Technical) (Batch reference number SEZ2BP007, purity = 96.5%) was admixed to the diet and fed to 10 Alpk:AP_iSD (Wistar-derived) rats per sex per dose at dose levels of 0, 100, 500, 3000 or 5000 ppm (0, 8.2, 41.1, 260.3, and 435.4 mg/kg/day, respectively for males and 0, 8.9, 44.7, 260.4, and 443.5 mg/kg/day, respectively for females) for at least 90 consecutive days. No animals died during the study. No treatment-related clinical signs were observed. A treatment-related decrease in adjusted mean body weight (determined by analysis of covariance) was observed in males at 3000 and 5000 ppm. Treatment-related decreases in mean hematocrit and hemoglobin levels were observed in females at 3000 and 5000 ppm; a treatment-related decrease in the mean hemoglobin level was observed in males at 5000 ppm. Treatment-related decreases in mean cell volume, mean cell hemoglobin, and mean cell hemoglobin concentration

levels were observed in both sexes at 3000 and 5000 ppm. A treatment-related increase in the mean γ -glutamyl transferase level in females at 3000 and 5000 ppm was observed. Urinalysis revealed no treatment-related effects. A treatment-related increase in liver weight adjusted to body weight (determined by analysis of covariance) was observed in both sexes at 3000 and 5000 ppm. Microscopic examination revealed a treatment-related increase in eosinophilia and hypertrophy of the periportal hepatocytes in males at 5000 ppm and in females at 3000 and 5000 ppm. **No adverse effects.** NOEL (M) = 41.1 mg/kg/day (500 ppm) and NOEL (F) = 44.7 mg/kg/day (500 ppm) based on an increase in liver weight and an increase in eosinophilia and hypertrophy of the periportal hepatocytes. **Acceptable.** (Corlett, 01/25/08)

Rat Subchronic Neurotoxicity Study

0121, 230441; "NOA 446510: Subchronic Neurotoxicity Study in Rats" (Pinto, P.J., Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Laboratory Project ID: Report Number CTL/PR1294/Regulatory/Report, Syngenta Number T008126-03, 11/15/05). 870.6200. NOA 446510 (Technical) (Batch reference number SEZ2BP007, purity = 96.5%) was admixed to the diet and fed to 12 Alpk:AP_rSD (Wistar-derived) rats per sex per dose at dose levels of 0, 100, 500, or 2500 ppm (0, 7.4, 37.3, and 192.5 mg/kg/day, respectively for males and 0, 8.4, 41, and 206.7 mg/kg/day, respectively for females) for at least 90 consecutive days. No animals died during the study. No treatment-related clinical signs were observed. A treatment-related decrease in adjusted mean body weight (determined by analysis of covariance) was observed in males at 2500 ppm. FOB and motor activity assessments revealed no treatment-related effects. A treatment-related increase in mean liver weight adjusted to body weight (determined by analysis of covariance) was observed in both sexes (non-perfused animals) at 2500 ppm. Neuropathological examination on the central and peripheral nervous systems revealed no treatment-related effects. No evidence of neurotoxicity was indicated. **No adverse effects.** NOEL (M) = 37.3 mg/kg/day (500 ppm) and NOEL (F) = 41 mg/kg/day (500 ppm) based on an increase in liver weight. **Acceptable.** (Corlett and Leung, 02/04/08)

Rat Preliminary Multiple Dosing Dermal Toxicity Study

0102; 230421; "NOA446510: Dose Range Finding Study in the Rat (For 28 Day Dermal Toxicity Study)" (Lees, D., Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Laboratory Project ID: Study Number CTL/LR0597/Technical Toxicology/Report Syngenta Number T008147-03, 12/20/05). NOA 446510 (technical) (Batch reference number SEZ2BP007, purity = 96.5%) was mixed with deionized water, applied to a foil backed gauze patch and placed onto the clipped dorso-lumbar region (held in place with a bandage) of 2 Alpk:AP_rSD (Wistar-derived) rats per sex per dose at dose levels of 0 (bandage only), 250, 500, and 1000 mg/kg/day for 6 hours on days 1-5 and on days 8-12 over a 14-day period. No mortalities occurred. No treatment-related clinical signs of systemic toxicity were observed. Erythema, edema, and/or desquamation were observed in all treated animals. Examination of body weight and food consumption data revealed no treatment-related effects. No effects on liver weight were observed. Macroscopic examination revealed treatment-related scabs on the skin in both sexes at 500 and 1000 mg/kg/day. **No adverse effects.** NOEL (M/F, systemic) = 1000 mg/kg/day based on no effects at the highest dose tested; NOEL (M/F, skin) could not be determined since edema was observed in all animals tested. **Supplemental study** (only 2 animals per sex per dose level were used and the test animals were dosed only 10 times over a 14-day period). (Corlett, 03/14/08)

Rat 28-Day Multiple Dosing Dermal Toxicity Study

0103, 230422; "NOA 446510: 28 Day Dermal Toxicity in Rats" (Lees, D., Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Laboratory Project ID: Study Number CTL/LR0596/Regulatory/Report Syngenta Number T004582-02, 11/16/05). 870.3200. NOA 446510 (Technical) (Batch reference number SEZ2BP007, purity = 96.5%) was mixed with deionized water, applied to a foil backed gauze patch and placed onto the clipped dorso-lumbar region (held in place with a bandage) of 10 Alpk:AP_rSD (Wistar-derived) rats per sex per dose at dose levels of 0 (bandage only), 250, 500, and 1000 mg/kg/day for 6 hours on 21 days of a 28 day study period. No treatment-related mortalities occurred. No treatment-related systemic clinical signs were observed. Treatment-related erythema and edema were observed in all

treated animals. Examination of body weight and food consumption data revealed no treatment-related effects. Hematology, serum chemistry, and urinalysis revealed no treatment-related effects. FOB and motor activity assessments revealed no treatment-related effects. No treatment-related effects on organ weights were observed. Macroscopic and microscopic examinations revealed no treatment-related abnormalities. **No adverse effects.** NOEL (M/F, systemic) = 1000 mg/kg/day based on no effects at the highest dose tested; NOEL (M/F, skin) could not be determined since erythema and edema were observed at all dose levels tested. **Acceptable.** (Corlett, 03/21/08)

Mouse 4-Week Dietary Toxicity Study

0098, 230417; "NOA 446510: 28 Day Dietary Range Finding Study in Mice" (Milburn, G., Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Laboratory Project ID: Study Number CTL/KM1473/Technical Toxicology/Report Syngenta Number T005180-01, 12/20/05). 870.3050. NOA 446510 (Technical) (Batch reference number KI-6380/6, purity = 98.5%) was admixed to the diet and fed to 5 C57BL/10J_rCD-1 mice per sex per dose at dose levels of 0, 700, 2100, or 7000 ppm (0, 108.2, 319.0, and 1411.4 mg/kg/day, respectively for males and 0, 122.2, 378.0, and 1349.7 mg/kg/day, respectively for females) for 28 consecutive days. No treatment-related mortalities occurred. No treatment-related clinical signs were observed. A treatment-related decrease in adjusted mean body weight (determined by analysis of covariance) was observed in males at 7000 ppm and in females at 2100 and 7000 ppm. Treatment-related decreases in mean hematocrit and hemoglobin levels were observed in males at 7000 ppm and in females at 2100 and 7000 ppm; treatment-related decreases in mean cell volume and mean cell hemoglobin were observed in both sexes at 2100 and 7000 ppm. A treatment-related increase in liver weight adjusted to body weight (determined by analysis of covariance) was observed in both sexes at 2100 and 7000 ppm. Microscopic examination revealed a treatment-related increase in eosinophilia and hypertrophy of the periportal hepatocytes in both sexes at 7000 ppm. **No adverse effects.** NOEL (M) = 108.2 mg/kg/day (700 ppm) and NOEL (F) = 122.2 mg/kg/day (700 ppm) based on an increase in liver weight and an increase in eosinophilia and hypertrophy of the periportal hepatocytes. **Acceptable.** (Corlett, 02/07/08)

Mouse Subchronic Dietary Toxicity Study

0094, 230413; "NOA 446510: 90 Day Dietary Range Finding Study in the Mouse" (Milburn, G., Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Laboratory Project ID: Study Number: PM1265, Syngenta Number: T004588-02, 12/20/05). 870.3100. NOA 446510 (Technical) (Batch reference number SEZ2BP007, purity = 96.5%) was admixed to the diet and fed to 10 C57BL/10J_rCD-1 mice per sex per dose at dose levels of 0, 300, 800, 2000, or 5000 ppm (0, 37.2, 98.0, 247.6, and 624.3 mg/kg/day, respectively for males and 0, 47.3, 128.9, 315.8, and 800.5 mg/kg/day, respectively for females) for at least 90 consecutive days. No animals died during the study. No treatment-related clinical signs were observed. A treatment-related decrease in adjusted mean body weight (determined by analysis of covariance) was observed in males at 2000 and 5000 ppm and in females at 5000 ppm. Treatment-related decreases in mean hematocrit and hemoglobin levels were observed in males at 5000 ppm and in females at 2000 and 5000 ppm; treatment-related decreases in mean cell volume and mean cell hemoglobin were observed in females at 800 ppm and in both sexes at 2000 and 5000 ppm. A treatment-related increase in liver weight adjusted to body weight (determined by analysis of covariance) was observed in both sexes at 800, 2000 and 5000 ppm. Microscopic examination revealed a treatment-related increase in eosinophilia of the periportal hepatocytes in females at 2000 ppm and in both sexes at 5000 ppm. **No adverse effects.** NOEL (M) = 37.2 mg/kg/day (300 ppm) and NOEL (F) = 47.3 mg/kg/day (300 ppm) based on an increase in liver weight and an increase in eosinophilia of the periportal hepatocytes. **Acceptable.** (Corlett, 02/14/08)

Dog Preliminary Oral and Dietary Toxicity Study

0101; 230420; "NOA446510: Preliminary Oral Toxicity Study in Dogs" (Brammer, A., Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Laboratory Project ID: Study Number CTL/KD1474/Technical Toxicology/Report Syngenta Number T005184-01, 12/19/05). NOA 446510 (technical) (Batch reference number KI-6380/6, purity = 98.5%) was administered by

capsule or diet to one beagle dog per sex per dose at dose levels of 0 (control diet and empty capsules), 100 (days 1-7), 300 (days 8-14), and 1000 mg/kg/day (days 15-21) (capsules and control diet), and 3000 (days 1-7) and 10000 ppm (days 8-21) (test diet and empty capsules) for up to 21 days. No mortalities occurred. The male and female dogs dosed with 3000/10000 ppm were observed to be thin. The male and female dogs dosed with 3000/10000 ppm lost weight and consumed less food than the control and low dose animals. A slight decrease in white blood cell and neutrophil counts was observed in the male and female dogs dosed with 3000/10000 ppm at week 4 compared to the control and low dose animals. An increase in plasma alkaline phosphatase and alanine aminotransferase levels was observed in the male dog dosed with 100/300/1000 mg/kg/day and in the male and female dogs dosed with 3000/10000 ppm at weeks 3 and 4 and in the female dog dosed with 100/300/100 mg/kg/day at week 4 compared to the control animals. Urinalysis revealed no treatment-related effects. Toxicokinetic parameters assayed included Tmax, Cmax, and AUC: Tmax values ranged from 3 to 8 hours, Cmax values ranged from 1.68 µg/mL (100 mg/kg) to 16.3 µg/mL (10000 ppm), and AUC values ranged from 23.1 hr.µg/mL (100 mg/kg) to 312 hr.µg/mL (10000 ppm). A treatment-related increase in relative liver weight was observed in the male at 1000 mg/kg and in females at 1000 mg/kg and 10000 ppm. Microscopic examination revealed a treatment-related accumulation of brown pigment within the hepatocytes and Kupffer cells in both sexes at 1000 mg/kg and 10000 ppm, increased single cell necrosis in the liver in the female at 10000 ppm, and reduced glycogen in the liver (periportal) in the male at 10000 ppm and in the females at 1000 mg/kg and at 10000 ppm. **No adverse effects.** NOEL (M/F) could not be assigned. **Supplemental study** (only 1 animal per sex per dose level was used and the test animals were dosed for only 21 days). (Corlett, 02/22/08)

Dog 6-Week Oral Toxicity Study

0100; 230419; "NOA446510: 6 Week Preliminary Oral Toxicity Study in Dogs" (Brammer, A., Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Laboratory Project ID: Study Number CTL/KD1519/Technical Toxicology/Report Syngenta Number T004600-02, 12/16/05). NOA 446510 (technical) (Batch reference number SEZ2BP007, purity = 96.5%) was administered by gelatin capsules to one beagle dog per sex per dose at dose levels of 0 (empty gelatin capsules), 100, 200, 400, and 800 mg/kg/day daily for at least 6 weeks. No mortalities occurred. No treatment-related clinical signs were observed. The male dog dosed with 800 mg/kg/day gained less weight and consumed less food than the other male dogs. A slight decrease in white blood cell and neutrophil counts was observed in the female dog dosed with 800 mg/kg/day at week 6 compared to the other female dogs. An increase in the plasma alkaline phosphatase level was observed in both sexes at all dose levels at weeks 3 and 6 and an increase in the alanine aminotransferase level was observed in males at 400 and 800 mg/kg/day at weeks 3 and 6 and in females at 800 mg/kg/day at week 6. Urinalysis revealed no treatment-related effects. Toxicokinetic parameters assayed included Tmax, Cmax, and AUC: Tmax values ranged from 3 to 8 hours, Cmax values ranged from 1.77 µg/mL (200 mg/kg, male, day 1) to 15.1 µg/mL (800 mg/kg, male, week 6), and AUC values ranged from 11.4 hr.µg/mL (100 mg/kg, male, day 1) to 202 hr.µg/mL (800 mg/kg, male, week 6). A treatment-related increase in liver to body weight ratio was observed in males at doses of 200 mg/kg/day and above and in females at all dose levels. Microscopic examination revealed treatment-related hepatocyte and/or macrophage/Kupffer cell pigmentation in the liver in both sexes at all dose levels. **No adverse effects.** NOEL (M/F) could not be assigned. **Supplemental study** (only 1 animal per sex per dose level was used and the test animals were dosed for only 6 weeks). (Corlett, 02/27/08)

Dog Subchronic Oral Toxicity Study

0099; 230418; "NOA446510: 90 Day Oral Toxicity Study in Dogs" (Brammer, A., Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Laboratory Project ID: Study Number CTL/PD1272/Regulatory/Report Syngenta Number T004586-02, 10/13/05). 870.3150 NOA 446510 (technical) (Batch reference number SEZ2BP007, purity = 96.5%) was administered by gelatin capsules to 4 beagle dogs per sex per dose at dose levels of 0 (empty gelatin capsules), 5, 25, 100, and 400 mg/kg/day daily for at least 90 consecutive days. No mortalities occurred. No treatment-related clinical signs were observed. Examination of body weight and food consumption data revealed no treatment-related effects. A treatment-related increase in the mean plasma alkaline phosphatase level was observed in both sexes at 400 mg/kg/day at weeks

4, 8, and 13 and in males at 100 mg/kg/day at weeks 4 and 13 and in females at 100 mg/kg/day at week 13; a treatment-related increase in the mean alanine aminotransferase level was observed at 400 mg/kg/day in both sexes (at weeks 8 and 13 in males and at weeks 4, 8, and 13 in females) (determined by analysis of covariance). Urinalysis revealed no treatment-related effects. A treatment-related increase in liver weight adjusted to body weight (determined by analysis of covariance) was observed in males at 100 and 400 mg/kg/day and in females at 400 mg/kg/day. Microscopic examination revealed treatment-related hepatocyte and/or macrophage/Kupffer cell pigmentation in the liver in both sexes at 100 and 400 mg/kg/day. **No adverse effects.** NOEL (M/F) = 25 mg/kg/day based on an increase in liver weight, elevation in liver enzymes, and pigment deposition in the liver. **Acceptable.** (Corlett, 03/12/08)

STUDIES ON METABOLITES

Gene Mutation

53030-0141 230461, "SYN 500003 (Metabolite of NOA446510): Bacterial Mutation Assay in *S. Typhimurium* and *E. Coli*, Final Report", (R. D. Callander, Syngenta Central Toxicology Laboratory, Macclesfield, Cheshire, UK., Report No. YV7195/Regulatory/Report, 16 February 2006). Triplicate cultures (5 solvent control cultures) of *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strains WP2 and WP2 *uvrA* were exposed to SYN 500003 (metabolite of NOA446510) (99% purity), in the presence and absence of S9 mix, at 0 (DMSO), 100, 200, 500, 1000, 2500 and 5000 ug/plate for 3 days using direct plate incorporation. In an additional assay using the same treatment levels, direct plate incorporation was used in the absence of S9 mix and preincubation (treatment for 60 minutes prior to plate incorporation and 3 day incubation) was used in the presence of activation. The numbers of revertant colonies were not increased by treatment. Reduced background lawn growth and a decrease in the number of revertants were noted for most strains at the high dose level in the absence of activation. Positive controls were functional. Supplemental data. (Green and Leung, 4/16/08).

53030-0142 230462, "SYN545038 (Impurity of Mandipropamid): Bacterial Mutation Assay in *S. Typhimurium* and *E. Coli*, Final Report". D. Callander, Syngenta Central Toxicology Laboratory, Macclesfield, Cheshire, UK., Report No. YV7241-REG, 22 March 2006). Triplicate cultures (5 solvent control cultures) of *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strains WP2 and WP2 *uvrA* were exposed to SYN 545038 (98%), in the presence and absence of S9 mix, at 0 (DMSO), 20, 50, 100, 200, 500, 1000, 2500 or 5000 ug/plate for 3 days at 37° C using direct plate incorporation. A repeat assay was performed. The number of revertants per plate was not increased by treatment in the absence of activation. In the presence of S9 mix, significant dose-related increases in the number of revertants per plate were recorded for strains TA98, TA100, TA1535, TA1537 and WP2 *uvrA*. Precipitate was generally noted at 2500 and 5000 ug/plate, both in the presence and absence of S9, in all strains, and at 1000 ug/plate in TA1535 and TA1537 without activation. Positive controls were functional. Supplemental data. (Green and Leung, 4/16/08)