CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
Picoxystrobin

Chemical Code # 6061, Tolerance # 53149

4 January 2012
Revised date: May 21st, 2012

I. DATA GAP STATUS

Combined toxicity, rat:	No data gap, possible adverse effects
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, possible adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, possible adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

All record numbers through 263827 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
File name: T120104A prepared by H. Green, revised by R. Pan

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

COMBINED, RAT

****53149-0127, 0213 256720, 259049**, "Picoxystrobin (DPX-YT669) Technical: Combined Chronic Toxicity/Carcinogenicity Study 2-Year Feeding Study in Rats", (L. Craig, MPI Research, Inc., Mattawan, MI., Laboratory Project ID DuPont-26171, 7 April 2011). Seventy CD® [Crl:CD®(SD)] rats per sex per group received DPX-YT669 (picoxystrobin technical) (99.3%) in the diet for 103 to 105 weeks. Additional groups of 10 animals per sex per group (toxicity phase) were necropsied after 52 weeks of treatment. Group mean compound consumption over the entire treatment period was 2.2, 8.8, 45.3, and 162.1 mg/kg/day for males and 2.8, 11.0, 57.1, and 203.3 mg/kg/day for females at 50, 200, 1000, and 3500 ppm, respectively. A statistically significant increase in the survival rate was recorded for high dose males and females and for 1000 ppm females (attributed to lower bodyweights). An increased incidence of soft feces, statistically significant (Fisher's exact) in males, was noted at 1000 ppm (145 incidents/37 males and 26/8 females) and 3500 ppm (520/63 males and 47/17 females) vs controls (38/20 males and 10/4 females). A significant reduction in group mean bodyweight was recorded for high dose males and females during the treatment period vs controls. Group mean bodyweight change was reduced for high dose males (18%, ns) and females (28%, $p<0.05$) for treatment weeks -1 through 104/101, respectively vs controls. Group mean food consumption was significantly reduced for males (4%) and females (10%) through the first year of treatment vs controls. No treatment-related hematology, urinalysis, or necropsy results were indicated at any treatment level. At the interim sacrifice, group mean relative (% bodyweight) epididymides, kidney, and testes weights were significantly increased for high dose males vs controls. At terminal sacrifice, significant increases in group mean relative (% bodyweight) liver weights were noted for both sexes and in relative brain, heart, and uterus weights in females at 3500 ppm vs controls. Treatment-related histopathology results were noted. Neoplastic observations included a significant increased trend in testicular interstitial cell adenomas at 3500 ppm vs controls (7/70 vs 1/70) (4 of the 7 males had survived to terminal sacrifice (day 730), of the remaining 3, two were sacrificed *in extremis* (days 679 and 721), and the third was found dead (day 616) late in the study. Since survival was significantly increased in high dose males, a Peto test was conducted that indicated the increased incidence of interstitial cell adenomas remained statistically significant when increased survival was taken into account ($p=0.009$)). The historical control range for interstitial adenomas at this laboratory in 48 studies was 0% to 14% (only 1 study was at 14%, the remaining 47 studies were at 8.3% or below (lower than the 10% incidence at the high dose in this study). Non-neoplastic lesions included a significantly increased incidence of testicular interstitial cell hyperplasia in high dose males vs controls (8/70 vs 1/70) (all animals with interstitial cell hyperplasia survived to terminal sacrifice and the incidence (11.4%) was outside the laboratory historical control range (0% to 1.5%). Record 256720 is the 1year interim report of this study. Chronic NOEL = 1000 ppm (45.3 mg/kg/day for males and 57.1 mg/kg/day for females) based on reduced bodyweight, food consumption, and increased incidence of interstitial cell hyperplasia and benign adenoma in the testes. **Possible adverse effect**: an increased incidence of testicular interstitial cell adenomas in males. Acceptable. (Green and Leung, 7/7/11).

****53149-0114, 0128 256707, 256730**, "ZA1963: 2 Year Dietary Toxicity and Oncogenicity Study in Rats", **(**N.J. Rattray, Zeneca Central Toxicology Laboratory, Alderley Park Macclesfield, Cheshire, UK., Report No. CTL/P/5963, 1 February 1999). 52 Alpk:AP_fSD rats per sex per group received ZA1963 (picoxystrobin technical) (93.3%) in the diet at 0 (basal diet), 50, 200, and 750 ppm for 104 weeks. Additional groups of 12 animals per sex per group (toxicity phase) were necropsied after 52 weeks of treatment. Group mean achieved dosages during the 104 week treatment period were 3.1, 12.2, and 45.6 mg/kg/day for males and 3.8, 14.8, and 57.8 mg/kg/day for females at 50, 200, and 750 ppm, respectively. Survival to terminal sacrifice was slightly increased in high dose males and in low, mid, and high dose females vs controls. Group mean

bodyweight was significantly reduced for high dose males (up to week 65) and females (throughout the treatment period) vs controls. At 750 ppm, group mean food consumption was significantly decreased for males (through treatment week 44 and most pronounced through week 10) and females (through week 68 and most pronounced through week 48) vs controls. At terminal sacrifice, there was a significant reduction in group mean relative kidney weights (% of bodyweight) in males and females at 750 ppm vs controls. Non-neoplastic findings included slight increases (ns) in *spongiosis hepatis* and glycogen accumulation (interim animals only) in the liver of high dose males. Neoplastic findings included an increased, statistically significant trend in the incidence of large granular cell leukemia in high dose males vs controls (the overall incidence was 2/64, 0/64, 3/64, and 7/64 for males and 5/64, 11/64, 4/64, and 2/64 for females at 0, 50, 200, and 750 ppm, respectively). The lesion was not present in any group at the interim sacrifice and the first incidence was recorded late in the treatment period, at week 97. Analysis showed no decrease in time to tumor for males treated with the test article. The increased incidence observed in males was slightly outside the top of the historical control range (7/52 vs 5/52) (the top of the historical control range for females was 11/52). There were no statistical differences in the intergroup comparison of overall tumor incidence in either sex. Volume 53149-0114, record 256707 is a 90-day rat feeding study used to set treatment levels. Chronic NOEL = 200 ppm (12.2 mg/kg/day for males and 14.8 mg/kg/day for females) based on reduced bodyweight and food consumption. **Possible adverse effect:** an increased incidence of large granular cell leukemia in high dose males. Acceptable. (Green and Leung, 5/26/11).

CHRONIC TOXICITY, DOG

**53149-0123 256716, "ZA1963: 1 Year Dietary Toxicity Study in Dogs", (D. Lees, Zeneca Central Toxicology Laboratory, Alderley Park Macclesfield, Cheshire, UK., Report No. CTL/P/6049, 18 January 1999). Four beagle dogs per sex per group received ZA1963 (picoxystrobin technical) (94.4%) in the diet at 0 (basal diet), 50, 150, and 500 ppm for one year. Group mean achieved dosing levels of ZA1963 in the diet during the treatment period were calculated as 1.6, 4.8, and 16.1 mg/kg/day for males and 1.6, 4.6, and 15.7 mg/kg/day for females at 50, 150, and 500 ppm, respectively. An increased incidence of thin appearance was recorded for males and females at 500 ppm compared to controls. Additionally, the incidence of reddened gums and fluid feces was increased in high dose males during the treatment period vs controls. Group mean bodyweight was significantly reduced for males (treatment weeks 2 to 30) and females (weeks 2 to 52) at 500 ppm vs controls. Significant reductions in group mean food consumption were recorded for both sexes throughout the treatment period at 500 ppm vs controls. Group mean relative thyroid weights were slightly increased (ns) for 500 ppm females vs controls. No treatment-related effects were noted for hematology, serum chemistry, urinalysis, necropsy results, or histology results. No adverse effect. Chronic NOEL = 150 ppm (4.8 mg/kg/day for males and 4.6 mg/kg/day for females) based on reduced bodyweight and food consumption. Acceptable. (Green and Leung, 6/6/11).

ONCOGENICITY, RAT

See combined, rat.

ONCOGENICITY, MOUSE

****53149-0125, 0212 256718, 259048,** "Picoxystrobin (DPX-YT669) Technical: Oncogenicity 18-Month Feeding Study in Mice", (Kyoung Sik Moon, Korea Institute of Toxicology, Yuseong-gu Daejeon, Republic of Korea, Report No. DuPont-24837, 11 April 2011). Sixty Crlj:CD1(ICR) mice per sex per group received DPX-YT669 (picoxystrobin technical) (99.3%) in the diet at 0 (basal diet), 100, 600, 2400, and 4800 ppm for 78 weeks. Group mean daily intake of DPX-YT669

during the treatment period was 12.1, 70.8, 293.3, and 583.2 mg/kg/day for males and 16.4, 98.6, 411.5, and 799.3 mg/kg/day for females at 100, 600, 2400, and 4800 ppm, respectively. A statistically significant increase in survival was recorded at 2400 and 4800 ppm for males vs controls (83% of males and 72% of females at 2400 ppm and 93% of males and 75% of females at 4800 ppm survived to terminal sacrifice compared to 72% of control males and 78% of control females). Group mean relative (% bodyweight) liver weights were significantly increased for high dose males (22%) and females (31%) compared to controls and for females at 2400 ppm (26%) (male liver weights at 2400 ppm were also increased (16%, ns)). In males, the incidence of liver masses/nodules was increased at 2400 ppm (27/60) and 4800 ppm (29/60) compared to controls (20/60). Non-neoplastic histology was seen in both males and females. In males, an increased incidence and severity of duodenal mucosal hyperplasia was noted at 2400 ppm (6/59, ns) and 4800 ppm (10/58, $p<0.05$) vs controls (3/50). In liver, centrilobular hepatocellular hypertrophy was increased in females at 2400 ppm (5/60, ns) and 4800 ppm (28/60, $p<0.05$) vs controls (2/60) (the hypertrophy was characterized as an increase in cytoplasmic volume, not nuclear size, and consistent with an adaptive induction of hepatocellular enzyme systems secondary to xenobiotic exposure rather than with evidence of hepatotoxicity). Neoplastic changes were reported in liver of males. The incidence of hepatic adenoma (single and multiple) and combined hepatic adenoma/carcinoma (animals with at least 1 hepatocellular neoplasm) was significantly increased (Cochran-Armitage trend test) in high dose males compared to controls (this was attributed to the increased survival rate in high dose males, rather than treatment, since: (1) the differences were not statistically significant using pair-wise comparison (Fisher's exact test) or survival adjusted statistics (Poly-3 test or Peto analysis), (2) there was no increase in multiple tumors, and (3) there was no progression of adenomas to carcinomas). The incidence of mixed liver foci of cellular alteration was also significantly increased in high dose males by the Cochran Armitage trend test but not by Fisher's exact test or when survival adjusted and, as with liver adenomas, was considered secondary to increased survival, rather than treatment related. Record 256718 contains unaudited in life data from the study when it was still in progress (5 April 2010). Chronic NOEL = 600 ppm (70.8 mg/kg/day for males and 98.6 mg/kg/day for females) based on increased relative liver weights. **Possible adverse effect**: An increased incidence of hepatocellular adenoma and combined hepatocellular adenoma/carcinoma in males. Acceptable. (Green and Leung, 7/12/11).

**53149-0126 256719, "ZA1963: 80 Week Carcinogenicity Study in Mice", (N.J. Rattray, Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK., Report No. CTL/P/5962, 22 January 1999). Fifty C57BL/10J_fAP Alpk mice per sex per group received ZA1963 (picoxystrobin technical) (93.3%) in the diet at 0 (basal diet), 50, 200, and 800 ppm for 80 weeks. Group mean achieved dosing levels of ZA1963 in the diet during the treatment period were calculated as 6.6, 26.2, and 108.8 mg/kg/day for males and 8.8, 35.9, and 144.7 mg/kg/day for females at 50, 200, and 800 ppm, respectively. Group mean bodyweight and bodyweight gain were significantly reduced for males and females at 800 ppm for most treatment weeks during the study vs controls. Group mean relative liver weights were slightly increased (9% (ns)) for 800 ppm males vs controls (values for females were 2% higher than controls). Necropsy results included an increase in ulcerations in the stomach of high dose females vs controls (4/50 with ulcerated glandular stomach, 1/50 with ulcerated non-glandular stomach vs 0/50) (ns). Non-neoplastic histology results included an increased incidence of inflammation (8/50 vs 4/50) and erosion (7/50 vs 3/50) of the non-glandular stomach in high dose females vs controls (ns). Neoplastic histopathology results were unremarkable. No treatment-related effects were indicated for clinical signs, food consumption, or mortality. Chronic NOEL = 200 ppm (26.2 mg/kg/day for males and 35.9 mg/kg/day for females) based on reduced bodyweight and bodyweight gain. Carcinogenicity NOEL = 800 ppm (108.8 mg/kg/day for males and 144.7 mg/kg/day for females). No adverse effect. Acceptable. (Green and Leung, 6/9/11).

REPRODUCTION, RAT

**53149-0121 256714, “Oral (Diet) Two-Generation (One Litter per Generation) Reproduction Toxicity Study of Picoxystrobin (DPX-YT669) Technical in Rats”, (J.F. Barnett, Jr., Charles River Laboratories, Preclinical Services, Horsham, PA., Study No. Dupont-24867, 14 April 2010). Thirty F0 and F1 Crl:CD(SD) rats per sex per group received DPX-YT669 technical (picoxystrobin technical) (99.3%) in the diet at 0 (basal diet), 75, 300, 1000, and 2500 ppm through 2 generations with 1 litter per generation. Group mean consumed dosages for F0 males during the treatment period were 4.0, 15.8, 52.2, and 130.0 mg/kg/day at 75, 300, 1000, and 2500 ppm, respectively. Values for F0 females were 5.4, 21.7, 70.3, and 173.4 mg/kg/day during the precohabitation period; 5.1, 19.7, 66.5, and 163.1 mg/kg/day during gestation; and 10.1, 39.6, 127.3, and 297.2 mg/kg/day during lactation at 75, 300, 1000, and 2500 ppm, respectively. Group mean consumed dosages for F1 males during the treatment period were 5.3, 21.2, 71.0, and 187.7 mg/kg/day at 75, 300, 1000, and 2500 ppm, respectively. Group mean consumed dosages for F1 females were 7.9, 31.6, 106.3, and 273.1 mg/kg/day during the precohabitation period; 5.7, 22.6, 74.9, and 189.9 mg/kg/day during gestation; and 10.1, 42.5, 139.5, and 353.9 mg/kg/day during lactation at 75, 300, 1000, and 2500 ppm, respectively. One high dose F0 male was sacrificed *in extremis* (ataxia, vocalization to touch, and red stained fur and penis) on treatment day 92 and two F0 females were found dead, one at 300 ppm on gestation day 20 (no clinical signs preceded death) and, the other, at 1000 ppm on gestation day 22 (dystocia was indicated). At 2500 ppm, one F1 male was found dead on *postpartum* day (ppd) 26 after 3 days of exposure to treated diet (necropsy revealed red and dark red mottled lungs) and one F1 female was euthanized with ataxia and hunched posture on ppd 27 after 4 days of treatment. No treatment-related clinical signs were noted for F0 males and females and F1 females at any treatment level vs controls. A significant increase in the number of F1 males with mild dehydration was noted at 2500 ppm vs controls. Group mean bodyweight and bodyweight gains were significantly reduced for F0 males (entire treatment period) and females (bodyweight during premating, gestation, and lactation periods and bodyweight gain during the premating period) at 2500 ppm vs controls. Significant reductions in group mean bodyweight and bodyweight gains were noted for high dose F1 males during the treatment period vs controls. Group mean bodyweights were significantly reduced for F1 females at 1000 ppm on premating days 23 and 30 vs controls. At 2500 ppm, F1 female bodyweights were significantly reduced for most intervals during the premating, gestation, and lactation periods. Group mean absolute food consumption (g/day) was significantly reduced for F0 and F1 males (during the treatment period), for F0 females (during the premating, gestation, and lactation periods), and for F1 females (during premating and gestation) at 2500 ppm and for F1 females at 1000 ppm during the first week of premating vs controls. Group mean relative food consumption (g/kg/day) was significantly reduced during the first week of treatment for F0 males and females and during the lactation period for F0 females at 2500 ppm vs controls. F1 group mean relative food consumption was significantly increased for high dose males (during the treatment period) and for high dose females (for premating days 30-37 and 37-44) vs controls (values for high dose females were comparable to controls during gestation and lactation). Necropsy results for F0 and F1 parents at all treatment levels were unremarkable. Group mean relative (% bodyweight) liver weights were significantly increased for F0 and F1 males and females at 2500 ppm and for F0 males at 1000 ppm vs controls. Group mean relative weights for pituitary, thymus, right ovary, and uterus with oviduct and cervix in F0 females were significantly reduced at 2500 ppm vs controls. In F1 males at 2500 ppm, significant increases were noted for group mean relative weights of the left epididymis, left cauda epididymis, and seminal vesicles with fluid vs controls. At 2500 ppm, significant decreases in group mean relative left ovary and thyroid weights were noted for F1 females vs controls. F0 and F1 sperm parameters for males in all treated groups were comparable to controls. All F0 and F1 mating and fertility parameters for all treated groups were comparable to control values. Histopathology revealed an increased incidence of decreased cellularity (minimal to moderate atrophy) of cortical and medullary lymphoid tissue in the thymus of high dose F0 females vs controls (11/30 vs 0/30). Histology results for F0 males and F1 males and females were unremarkable. F1a group mean pup weights were significantly reduced at 1000 ppm (lactation day 22) and 2500 ppm (lactation

days 8, 15, and 22) vs controls. Group mean time to vaginal opening of F1 females was significantly delayed at 2500 ppm vs controls (36.4 days vs 32.8 days) (the value was outside the test facility historical control range (30.1 days to 35.3 days), however, the delay was not significant when individual bodyweight was used as a covariant in analysis of covariance, suggesting a result/manifestation of reduced F1a pup growth). Group mean F2a pup weights were significantly decreased at 2500 ppm for lactation days 15 and 22 vs controls. Group mean absolute and relative (% brain weight) thymus, spleen, and fixed thyroid gland weights were significantly reduced for F1a and F2a male and female pups at 2500 ppm vs controls (adrenal weights were also reduced for F1a pups). Additionally, group mean absolute and relative (% brain weight) spleen weights were significantly reduced for F1a female pups at 1000 ppm vs controls. No treatment-related F1a or F2a pup clinical signs or necropsy results were indicated. Parental NOEL = 300 ppm (15.8 mg/kg/day (F0 males) and 21.2 mg/kg/day (F1males) and 21.7 mg/kg/day (F0 females (premating) and 31.6 mg/kg/day (F1 females (premating)) based on reduced bodyweight and increased liver weight. Pup NOEL = 300 ppm based on reduced pup growth. Reproductive NOEL = 2500 ppm (130.0 mg/kg/day (F0 males) 187.7 mg/kg/day (F1 males) and 173.4 mg/kg/day (F0 females (premating)) and 273.1 mg/kg/day (F1 females (premating)). No adverse reproductive effect. Acceptable. (Green and Leung, 6/27/11).

**53149-0122 256715, “ZA1963: Multigeneration Reproduction Study in Rats”, (G.M. Milburn, Zeneca Central Toxicology Laboratory, Alderley Park Macclesfield, Cheshire, UK., Report No. CTL/P/5764, 18 August 1998). Twenty-six F0 and F1 Alpk:AP_fSD rats per sex per group received ZA1963 (picoxystrobin technical) (93.3%) in the diet at 0 (basal diet), 50, 200, and 750 ppm through 2 generations with 1 litter per generation. Group mean achieved dosages during the premating period for F0 animals were 5.3, 21.2, and 78.2 mg/kg/day for males and 5.8, 23.3, and 85.5 mg/kg/day for females, and, values for F1 parents were 5.4, 21.8, and 81.8 mg/kg/day for males and 5.8, 23.5, 88.8 mg/kg/day for females at 50, 200, and 750 ppm, respectively. Significant reductions in group mean bodyweight were noted during the premating period for F0 and F1 males (from week 2) and females (from week 5 or 6) at 750 ppm and for F1 males at 200 ppm (from week 5) compared to controls. Group mean bodyweights were significantly reduced for F0 and F1 females on day 1 of the gestation and lactation periods at 750 ppm vs controls (bodyweights were generally comparable to controls at the end of the periods). Group mean food consumption was significantly reduced for F0 and F1 males (from week 1) and females (from week 3) during the premating period at 750 ppm vs controls. Significant premating reductions in group mean food consumption were also noted for F0 (weeks 2 and 3) and F1 (weeks 7 through 10) males at 200 ppm vs controls. Group mean relative liver weights were slightly increased (6.3% to 12.8% (ns)) for F0 and F1 males and females at 750 ppm compared to controls.

No treatment-related effects were indicated for F0 and F1 clinical signs, mortality, mating performance and fertility, gestation length, necropsy results, or histology results. Group mean pup weights were significantly reduced for F1a (post partum day 29) and F2a (post partum days 22 and 29) pups at 750 ppm during the lactation period vs controls. No treatment-related effects on F1a and F2a pup clinical observations, litter size, pup survival, organ weights, necropsy results, or histopathology results were recorded. Reproductive NOEL = 750 ppm (78.2 to 81.8 mg/kg/day for males and 85.5 to 88.8 mg/kg/day for females). Parental NOEL = 50 ppm (5.3 to 5.4 mg/kg/day for males and 5.8 mg/kg/day for females) based on reduced food consumption and bodyweight. Offspring NOEL = 200 ppm (21.2 to 21.8 mg/kg/day for males and 23.3 to 23.5 mg/kg/day for females) based on reduced pup weights. No adverse reproductive effect. Acceptable. (Green and Leung, 6/2/11).

TERATOLOGY, RAT

**53149-0120 256713, “ZA1963: Developmental Toxicity Study in the Rat”, (M.E. Moxon, Zeneca Central Toxicology Laboratory, Alderley Park Macclesfield, Cheshire, UK., Report No. CTL/P/4824, 2 April 1998). Twenty-four mated female Alpk:AP_fSD (Wistar-derived) rats per

group received ZA1963 (picoxystrobin technical) (99%) by oral gavage at 0 (corn oil), 10, 30, and 100 mg/kg/day on gestation days 7 through 16. One mid dose female was sacrificed on gestation day 10 following accidental injury. All remaining animals survived to scheduled sacrifice. Increased incidences of diarrhea and urine staining were recorded for 100 mg/kg/day females during the treatment period vs controls. Group mean maternal bodyweight was significantly reduced on gestation days 8 through 16 and 19 at 100 mg/kg/day compared to controls. Significant reductions in group mean food consumption were also recorded during the treatment period (gestation days 7 to 10, 10 to 13, and 13 to 16) for high dose dams vs controls. Minor skeletal defects included a significantly increased fetal incidence of unossified 3rd cervical centrum (32 (9.6%) vs 16 (5.2%)) and a significant increase in the number of litters with extremely misaligned 5th sternebra (5 (20.8%) vs 0 (0.0%)) at 100 mg/kg/day vs controls. Minor skeletal variants included a significant increase in the incidence of unossified odontoid (116 (32.6%) vs 59 (19.1%)), in partially ossified 5th sternebra (110 (30.9%) vs 67 (21.7%)), and with an unossified calcaneum (184 (51.7%) vs 118 (38.2%)) in fetuses at10 mg/kg/day vs controls(values at 30 and 100 mg/kg/day were comparable to controls). The incidence of fetuses with *manus* scores of 5 (33 (9.3%) vs 12 (3.9%)) and *pes* scores of 5 (137 (38.5%) vs 80 (25.9%)) (indicating reduced ossification) were significantly increased at 10 mg/kg/day vs controls (mid and high dose values were comparable to controls). Maternal NOEL = 30 mg/kg/day (reduced bodyweight and food consumption). Developmental NOEL = 100 mg/kg/day. No teratogenicity. Acceptable. (Green and Leung, 6/15/11).

TERATOLOGY, RABBIT

**53149-0210 256864, "ZA1963: Developmental Toxicity Study in the Rabbit", (M.E. Moxon, Zeneca Central Toxicology Laboratory, Alderley Park Macclesfield, Cheshire, UK., Report No. CTL/P/6034, 24 February 1999). Twenty time-mated female New Zealand White rabbits per group received ZA1963 (picoxystrobin technical) (93.3%) by oral gavage at 0 (1% carboxymethylcellulose), 8, 25, and 100 mg/kg/day on gestation days 8 through 20. An increased incidence of few feces and/or diarrhea was noted for does at 25 and 100 mg/kg/day vs controls. Group mean maternal bodyweight was significantly reduced for gestation days 9 through 13 at 100 mg/kg/day vs controls. Significant reductions in group mean maternal food consumption were noted for gestation days 8 through 11 (at 25 and 100 mg/kg/day) and 14 through 17 (at the high dose level) vs controls. The number of *corpora lutea* was reduced (ns) and pre-implantation loss was significantly increased (21% vs 12%) at 100 mg/kg/day vs controls. Minor fetal skeletal defects included a significant increase in the incidence of incomplete ossification of the odontoid in fetuses at 100 mg/kg/day vs controls (10 (9.0%) vs 1 (0.7%)). The incidence of fetal skeletal variants that were significantly increased included: fetuses with 13 thoracolumbar ribs of long length at the mid (86 (50.0%) vs 46 (32.4%)) and high dose levels (59 (53.2%)) and fetuses with 27 pre-pelvic vertebra (bilateral) at 100 mg/kg/day vs controls (44 (39.6%) vs 24 (16.9%)). All skeletal effects values were within their historical control ranges. Maternal NOEL = 25 mg/kg/day (reduced maternal bodyweight and food consumption). Developmental NOEL = 100 mg/kg/day. No teratogenicity. Acceptable. (Green and Leung, 6/14/11).

GENE MUTATION

**53149-0129 256731, "E1963: An Evaluation of Mutagenic Potential Using *S.Typhimurium* and *E. Coli*", (R.D. Callander, Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK., Report No. CTL/P/4827, 1 February 1996). Triplicate cultures (solvent controls were tested in quintuplicate, positive controls in duplicate) of *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strains WP2P and WP2P *uvr*A were exposed to E1963 (picoxystrobin technical) (93.3%), in the presence and absence of rat liver S9 mix, at 0 (DMSO), 100, 200, 500, 1000, 2500, and 5000 µg/plate for 72 hours (at 37°C). Direct

plate incorporation was used in the first trial. In the second trial, cultures treated in the presence of activation were preincubated for 1 hour prior to plating. There were no increases in the number of revertants per plate compared to solvent controls, in the presence and absence of activation, in either trial. Positive controls were functional. No adverse effect. Acceptable. (Green and Leung, 7/14/11).

****53149-0130 256732,** "E1963: L5178Y TK$^{+/-}$ Mouse Lymphoma Gene Mutation Assay", (P. Clay, Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK., Report No. CTL/P/4993, 22 April 1996). Duplicate cultures of L5178Y TK$^{+/-}$ mouse lymphoma cells were exposed to E1963 (picoxystrobin technical) (93.3%), in the presence and absence of rat liver S9 mix for 4 hours, at 0 (DMSO), 4, 8, 16, 24, 32, 42, 56, 64, or 75 μg/ml. Precipitation was reported at the high dose level in both phases 1 and 2 (64 and 75 μg/ml, respectively). Cytotoxicity (mean % survival relative to the solvent controls) at the high dose level was 62% (-S9 mix) and 71% (+S9 mix) in phase 1 and 61% (-S9 mix) and 33% (+S9 mix) in phase 2 vs controls. Dose related statistically significant increases in mutant frequency were recorded for activated cultures in both phases 1 and 2 (values were 200% to 300% of solvent control results and 44% to 66% of positive control values) yet small colony counts were comparable to solvent and positive controls, except in phase 2 (+S9), with small colony counts at the high dose level comparable to solvent controls but slightly increased vs positive controls. Additionally, in the absence of S9 mix, a dose related significant increase in mutant frequency was noted in phase 1, but not reproduced in phase 2. In the absence of activation, the mutant frequency was 0 at 64 μg/ml in phase 1 and at 56 and 75 μg/ml in phase 2. Positive controls were functional. **Possible adverse effect.** Acceptable. (Green and Leung, 7/19/11).

CHROMOSOME EFFECTS

**53149-0131 256733, "E1963: *In Vitro* Cytogenetic Assay in Human Lymphocytes", (V. Fox and J. Wildgoose, Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK., Report No. CTL/P/4973, 4 April 1996). Duplicate cultures of human whole blood (from 1 male (donor 1) and 1 female (donor 2)) were exposed, in the presence and absence of S9 mix, at E1963 (picoxystrobin technical) (93.3%) concentrations of 0 (DMSO), 0.5, 1.0, 2.5, 5.0, 7.5, 10, 15, 20, 30, 40, 50, or 60 μg/ml for 3 hours (activated cultures) and for 68 hours (non-activation). Cells were harvested 68 and/or 92 hours after the start of treatment. Cultures were treated with colcemid (0.4 μg/ml) 2 hours prior to harvest. Two hundred metaphases per concentration were scored. At the highest concentrations selected for chromosomal analysis, 60 μg/ml (donor 1) and 50 μg/ml (donor 2) with S9 mix and 5 μg/ml (both donors 1 and 2) without S9 mix, significant reductions in mean mitotic activity were noted vs controls at the 68 hour harvest interval (-57% +S9 mix and -58% -S9 mix for donor 1 and -51% +S9 mix and -54% -S9 mix for donor 2). Mean mitotic activity values at the 92 hour sampling for donor 2 were -20% at 50 μg/ml (+S9 mix) and +111% at 5 μg/ml compared to controls. No treatment-related increases in chromosomal aberrations were indicated for donor 1 or donor 2 lymphocyte cultures, in the presence and absence of S9 mix, at the 68 and 92 hour sampling times, compared to controls. Donor 2 cultures at 30 μg/ml (the mid dose analyzed) with activation showed a slight (statistically significant) increase in the mean percentage of cells with chromosomal aberrations vs solvent controls (6% vs 0.5%) (the positive control value was 36%). The effect was inconclusive since it was slight with no dose response (the value at the high dose analyzed (50 μg/ml) was 1.5%), and it was not reproduced in donor 1 cultures or at the 92 hour sampling of donor 2 cultures. No adverse effect. Positive controls were functional. Acceptable. (Green and Leung, 8/2/11).

**53149-0132 256734, "E1963: Mouse Bone Marrow Micronucleus Test", (D.A. Fox and J. M. Mackay, Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK., Report No. CTL/P/5008, 3 June 1996). Five CD-1 mice per sex per group received a single oral gavage dose of E1963 (picoxystrobin technical) (93.3%) at 0 (corn oil), 2000, 3200, and 5000 mg/kg followed by bone marrow sampling 24 or 48 hours later. All animals survived to sacrifice. No increases in micronucleated polychromatic erythrocytes (MPCEs) were recorded at the 24 hour sampling time at any treatment level for males and females nor for males at the 48 hour

sampling time vs controls. In high dose females, at the 48 hour sampling time, a slight but significant increase in incidence of MPCEs was noted vs solvent controls (2.7 vs 0.8 MPCEs/1000 PCEs at 5000 mg/kg vs controls (the positive control value was 31.0)). Subsequent evaluation of an additional 2000 PCEs per female at 5000 mg/kg (and for vehicle control females) yielded no increase in MPCEs. No increase in cytogenetic damage. Positive controls were functional. No adverse effect. Acceptable. (Green and Leung, 7/21/11).

DNA DAMAGE

**53149-0133 256735, "E1963: *In Vivo* Rat Liver Unscheduled DNA Synthesis Assay", (J.M. Mackay, Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK., Report No. CTL/P/5007, 5 June 1996). 5 male Alpk:AP_fSD rats per group (2 solvent and positive controls males per group) received a single oral gavage dose of E1963 (picoxystrobin technical) (93.3%) at 0 (corn oil), 3200, and 5000 mg/kg. Hepatocytes were sampled 2 and 16 hours after treatment. No mortality or toxicity was recorded after dosing. Viability of the hepatocytes was determined using trypan blue (the mean ranged from 73.5% to 75.4%). After attachment, cells were exposed to ^{3}H thymidine for 4 hours followed by at least 12 hours of incubation with unlabelled thymidine. Three autoradiographs per animal were prepared and 1 autoradiograph and 60 cells per animal were analyzed. There was no increase in the mean number of net nuclear grain counts. Positive controls were functional. No adverse effect. Acceptable. (Green and Leung, 8/9/11).

SUBCHRONIC STUDIES

Dog 90-Day Oral (Dietary) Toxicity Study

**53149-0209 256863, "ZA1963: 90 Day Dietary Toxicity Study in Dogs", (S.A. Horner, Zeneca Central Toxicology Laboratory, Alderley Park Macclesfield, Cheshire, UK., Report No. CTL/P/5643, 25 March 1998). Four beagle dogs per sex per group received ZA1963 (picoxystrobin technical) (94.4%) in the diet at 0 (basal diet), 125, 250, and 500 ppm for 90 days. Group mean achieved dosing levels of ZA1963 in the diet during the treatment period were calculated as 4.3, 8.9, and 16.5 mg/kg/day for males and 4.3, 8.5, and 16.9 mg/kg/day for females at 125, 250, and 500 ppm, respectively. At 500 ppm, treatment-related increases were indicated for the incidence of salivation at dosing in females (24 vs 4 for females and 8 vs 4 for males) and for fluid feces in males (18 vs 0 for males and 6 vs 1 for females) vs controls. Group mean bodyweight was significantly reduced for both sexes at 500 ppm for treatment weeks 2 to 14 and for mid dose males from weeks 5 to 14 (statistically significant only at week 7) vs controls. At 500 ppm, group mean food consumption was significantly reduced for males (through treatment week 10) and females (through week 11) during the treatment period vs controls. Group mean platelet counts were significantly increased for males at 250 ppm (treatment weeks 4 and 8) and 500 ppm (weeks 4, 8, and 13) vs controls. Significant reductions were noted in group mean plasma albumin and/or total protein levels for both sexes during treatment weeks 4, 8, and/or 13 at 500 ppm vs controls. Group mean relative kidney weights were increased (14%, ns) for males at 500 ppm vs controls (female values were 4% greater than controls). Additionally, group mean relative right kidney weights were increased (24%, ns) for high dose males vs controls (left kidney weights were 9% greater than controls) (right kidney weights for females were 4% greater than controls, left kidneys 9% greater). No treatment-related gross pathology results were indicated. Histology revealed an increase in minimal focal unilateral tubular dilatation with eosinophilic casts in kidneys of 500 ppm females vs controls (3/4 vs 0/4). Chronic NOEL for males = 125 ppm (4.3 mg/kg/day) reduced bodyweight.
Chronic NOEL for females = 250 ppm (8.5 mg/kg/day) reduced bodyweight and food consumption. No adverse effect. Acceptable. (Green, 6/7/11).

Rat 90-Day Oral (Feeding) Toxicity Study

**53149-0114 256707, "ZA1963: 90 Day Feeding Study in Rats", (N.J. Rattray, Zeneca Central Toxicology Laboratory, Alderley Park Macclesfield, Cheshire, UK., Report No. CTL/P/5588, 25 March 1998, revised 11 March 1999). Twelve Alpk:AP_fSD rats per sex per group received ZA1963 (picoxystrobin technical) (93.3%) in the diet at 0 (basal diet), 100, 500, and 1250 ppm for 90 days. Group mean calculated dose rates received during the study were 8.5, 41.7, and 104.9 mg/kg/day for males and 9.7, 48.1, and 120.1 mg/kg/day for females at 100, 500, and 1250 ppm, respectively. One high dose male was sacrificed for humane reasons in study week 7 (non-treatment related). All other animals survived to scheduled sacrifice. Group mean bodyweights for males and females were significantly reduced from study week 2 to the end of the treatment period at 1250 ppm compared to controls. Group mean food consumption was significantly reduced at the high dose level for males (weeks 1 through 10) and females (weeks 3 through 7, and 10) compared to controls. Group mean cell volume (males only) and group mean cell hemoglobin (both sexes) were significantly decreased at the mid and high dose levels vs controls. Significant reductions in group mean alkaline phosphatase, alanine and aspartate aminotransferase activities and triglycerides were noted for high dose males (alkaline phosphatase activity was also reduced in high dose females and mid dose males) compared to controls. Group mean absolute liver weights (after adjustment for terminal bodyweight by analysis of covariance) were significantly increased for both sexes at 1250 ppm and for 500 ppm males vs controls (group mean relative liver weights were also increased at these levels without statistical significance). No treatment-related effects were noted for clinical signs, ophthalmology, urinalysis, macroscopy, or histopathology. NOEL = 500 ppm (41.7 mg/kg/day for males and 48.1 mg/kg/day for females) based on reduced bodyweight and food consumption. No adverse effect. Acceptable. (Green, 5/9/11).

Rat 28-Day Dermal Toxicity Study

**53149-0117 256710, "Picoxystrobin (DPX-YT669) Technical: 28-Day Repeated-Dose Dermal Toxicity Study in Rats", (C. Carpenter, E.I. du Pont de Nemours and Company, DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE., Laboratory Project ID. DuPont-27314, 11 September 2009). Ten Crl:CD(SD) rats per sex per group were dermally treated (shaved, intact, occluded skin) with DPX-YT669 (picoxystrobin technical) (99.3%) at 0 (deionized water), 100, 300, and 1000 mg/kg/day 6 hours per day for 29 consecutive days. One male rat each at 100, 300, and 1000 mg/kg/day and one 300 mg/kg/day female died on test days 14, 9, 9, and 13, respectively (deaths were attributed to the wrapping procedures (overly tight)). No treatment-related effects were noted for mortality, clinical signs of toxicity, bodyweight, bodyweight gain, food consumption, dermal effects at application sites, hematology, clinical chemistry, ophthalmology, necropsy, or histopathology results. Dermal and Systemic NOEL (M/F) = 1000 mg/kg/day. No adverse effect. Acceptable. (Green, 5/18/11).

53149-0118 256711, "ZA1963: 28 Day Dermal Toxicity Study in Rats", (D. Lees, Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK., Report No. CTL/P/6192, 29 March 1999). Five Alpk:AP_fSD (Wistar-derived) rats per sex per group were dermally treated (clipped, intact, occluded skin) with DPX-YT669 (picoxystrobin technical) (99.3%) at 0 (deionized water), 200, 500, and 1000 mg/kg/day for 28 days (animals received 20 six hour applications over a 28 day period (test days 1-2, 5-9, 12-16, 19-23, and 26-28). All animals survived to scheduled termination. A slightly increased incidence of slight desquamation was noted for high dose males vs controls. Platelet count was slightly increased (statistically significant) for high dose females vs controls (values did not exceed the historical control range). Male platelet counts were generally comparable to controls at all treatment levels. No treatment-related effects were indicated for clinical signs, bodyweights, food consumption, serum chemistry, organ weights, gross pathology, or histopathology. Systemic NOEL > 1000 mg/kg/day. Supplemental data. (Green, 5/23/11).

Rat 28-day subacute inhalation toxicity study

53149-0216 263826, "Picoxystrobin (DPX-YT669) Technical: 28-day subacute inhalation toxicity study in Wistar rats"; Rat; International Institute of Biotechnology and Toxicity (IIBAT), Tamil Nadu, India, Laboratory Project ID: DuPont-32100, IIBAT Study #:10754, 12/16/11; Rajsekhar, P., Groups of 5 male and 5 female rats were exposed to nose only inhalation of test aerosol at 0 (control), 0.001, 0.01 or 0.025 mg/L (MMAD (GSD): 2.37 (2.72), 2.15 (2.77), and 2.12 (2.79), for 0.001, 0.01 and 0.025 mg/L groups, respectively) for 6 hours per day, 5 days per week for a total of 4 weeks exposure. Two additional groups of 5 male and 5 female rats were exposed to 0 (control) or 0.001 mg/L (MMAD (GSD): 2.61 (2.84)) test aerosol in the same manner with 2 weeks of recovery period. No mortality or moribundity was observed over the course of this study. There were no test substance-related clinical signs of toxicity in any of the animals during or after the 6-hour exposure. There were no treatment related changes in body weight, feed and water consumptions, hematology, clinical biochemistry, urinalysis, and pathology findings. **NOEL (No Observed Effect Level): 0.025 mg/L for male and female rats in this 28-day inhalation toxicity study. **Acceptable** (Pan & Leung, 5/17/12).

Mouse 90-Day Dietary Toxicity Study

53149-0115 256708, "ZA1963: 90 Day Feeding Study in Mice", (N.J. Rattray, Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK., Report No. CTL/T/2915, 26 June 1996). Ten C57BL/10J_fAP/Alpk mice per sex per group received ZA1963 (picoxystrobin technical) (99.0%) in the diet at 0 (basal diet), 200, 800, 1600, and 2400 ppm for 90 days. Group mean values for ZA1963 intake were 33.2, 137.2, 290.8, and 421.6 mg/kg/day for males and 43.8, 176.1, 358.5, and 534.8 mg/kg/day for females at 200, 800, 1600, and 2400 ppm, respectively. No treatment-related clinical observations were recorded. Group mean final bodyweights (day 92) were significantly reduced for males and females at 1600 and 2400 ppm and for 800 ppm females vs controls. Group mean food consumption (g/mouse/day) was significantly reduced for both sexes at 800, 1600, and 2400 ppm on treatment day 1 vs controls. Male food consumption at all treated levels was comparable to controls, thereafter. Subsequently, female food consumption was reduced from week 9 to the end of the study (with and/or without significance) at 800 ppm and higher compared to controls. Group mean relative (% bodyweight) liver weights were increased (ns) for both sexes at 800 ppm and higher compared to controls. Necropsy revealed an increased incidence of dark areas (3/10) and dark spots (1/10) in the spleen of high dose males vs controls (0/10). Histopathology effects included an increased incidence of minimal hepatocyte hypertrophy in livers of males and females at 1600 ppm (6/10 in each sex, $p < 0.05$ (Fisher's exact)) and 2400 ppm (4/10 in males (ns) and 9/10 in females, $p < 0.01$) and in females at 800 ppm (5/10 (ns)) vs controls (0/10). Additionally, an increased incidence of focal pigmentation of the spleen (4/10, ns) was noted in high dose males vs controls (0/10) (Perl's stain showed this to be negative for hemosiderin and was interpreted as melanin which is common in this heavily pigmented strain of mouse). NOEL = 200 ppm (33.2 mg/kg/day for males and 43.8 mg/kg/day for females) based on bodyweight and food consumption. An adverse effect was not indicated. Unacceptable and not upgradeable (no hematology, serum chemistry, or ophthalmology, incomplete histopathology). (Green, 6/29/11).

METABOLISM STUDIES

**53149-0138, 0139, 0140, 0141 256742, 256744, 256745, 256746, "ZA1963: Biotransformation in the Rat", (D. Macpherson, Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK., Report No. CTL/P/5346, 9 March 1999). Three Alpk:AP_fSD (Wistar-derived) rats per sex per group received a single oral gavage dose of [^{14}C]-phenylacrylate-ZA1963 or [^{14}C]-pyridinyl-ZA1963 at 100 mg/kg. Additionally, 2 bile duct cannulated rats per sex per group received [^{14}C]-phenylacrylate-ZA1963 or [^{14}C]-pyridinyl-ZA1963 by oral gavage at 100 mg/kg. Urine and feces were collected 6 (urine only), 12, 24, 36, 48, 72, 96, or 120 hours post treatment from non-cannulated animals. For cannulated animals, bile was sampled 2, 4, 6, 8, 12,

24, 36, and 48 hours and urine and feces 6 (urine only), 12, 24, 36, and 48 hours post dosing. The proportions of radiolabel excreted in bile, urine, and feces were determined. Metabolites were quantified in urine, feces, and bile for the bile duct cannulated rats in this study and in urine and feces from the [^{14}C]-phenylacrylate-ZA1963 low dose study (record 256744) (single dose at 10 mg/kg); high dose study (record 256745) (single dose at 100 mg/kg); and repeat dose study (record 256746) (single dose at 10 mg/kg following 14 consecutive daily doses of unlabeled ZA1963) (see one liners below in this worksheet, Section IV, B.). During 72 hours after a single oral gavage dose of [^{14}C]-phenylacrylate-ZA1963 at 100 mg/kg (Group A animals), 70.4% (males) and 58.3% (females) of radiolabel was excreted in feces and 15.2% (males) and 17.5% (females) was eliminated in urine and, during 120 hours (Group B animals), fecal excretion accounted for 65.7% (males) and 59.5% (females) of radiolabel and urine contained 25.9% (males) and 27.2% (females) of radioactive dose. After a single oral gavage dose of [^{14}C]-pyridinyl-ZA1963 at 100 mg/kg, rats excreted 72.2% (males) and 72.6% (females) of dose in feces and 20.0% (males) and 17.9% (females) of radioactivity in urine during 72 hours (Group C animals) and, during 120 hours post dosing (Group D animals), feces contained 70.8% (males) and 59.0% (females) of dose and urine had 18.8% (males) and 27.5% (females) of radiolabel.
Bile duct cannulated rats administered a single oral gavage dose of [^{14}C]-phenylacrylate-ZA1963 at 100 mg/kg excreted 30.9% (males) and 19.6% (females) of dose in feces; 2.0% (males) and 23.8% (females) in urine; and 71.4% (males) and 45.0% (females) of dose in bile during 48 hours post treatment (Group E animals). Bile duct cannulated rats that received a single oral gavage dose of [^{14}C]-pyridinyl-ZA1963 at 100 mg/kg excreted 18.0% (males) and 21.2% (females) of dose in feces; 4.5% (males) and 16.9% (females) in urine; and biliary elimination accounted for 71.8% (males) and 65.8% (females) of dose during 48 hours post dosing (Group F animals).

Bile was the predominant route of elimination of ZA1963 metabolites in both sexes of bile duct cannulated rats that received [^{14}C]-phenylacrylate-ZA1963 and [^{14}C]-pyridinyl-ZA1963 (metabolites were quantified for animals that received [^{14}C]-pyridinyl-ZA1963 since it represented both radiolabeled forms because no evidence of cleavage between the phenyl and pyridinyl rings was observed in bile. [^{14}C]-phenylacrylate-ZA1963 biliary metabolites were used during qualitative identification). Metabolite 40 (glucuronidyl (E)-3-methoxy-2-{2-[6-(trifluoromethyl)pyridine-2-yloxymethyl]phenyl} acrylate) was the major metabolite in bile, representing 28.87% (males) and 30.14% (females) of administered dose; metabolite 46 (methyl (E) 3-glucuronidyl-2-{2-[6-(trifluoromethyl)pyridin-2-yloxymethyl]phenyl}acrylate) and isomers of metabolite 49 (methyl 2-hydroxy-3-glucuronidyl-2-{2-[6-(trifluoromethyl)pyridin-2-yloxymethyl}phenyl}propionate) accounted for 20.1% (females) to 22.18% (males); and metabolite 43 (methyl (E)-2-{4-glucuronidyl-2-[6-(trifluoromethyl)pyridin-2-yloxymethyl]phenyl}-3-methyoxyacrylate) was present at ~6% (both sexes) (the remaining biliary metabolites represented less than 5% of dose and the profiles were similar between the sexes (except metabolite 44 (methyl (E)-3-hydroxy-2-{4-hydroxy-2-[6-trifluoromethyl)pyridin-2-yloxymethyl]phenyl}-3-methoxyacrylate) and unknown A were only present in male bile)). All of the radioactivity excreted in feces (18.0% (males) and 21.2% (females) of dose) was identified as unchanged ZA1963. In urine, there were pronounced differences in the profiles of metabolites between the 2 radiolabeled forms of ZA1963, representing cleavage between the phenyl and pyridinyl rings to give various single ring metabolites. After a single oral gavage dose of [^{14}C]-phenylacrylate-ZA1963 at 100 mg/kg, male urine contained 3 metabolites representing slightly less than 2% of administered radiolabel: metabolite 44 at 1.31% of dose, metabolite 51 (2,3-dihydroxy-2-{2-[6-(trifluoromethyl)pyridin-2-yloxymethyl]phenyl}propionic acid) at 0.37% of dose, and metabolite E (unidentified) at 0.3% of dose. In contrast, female [^{14}C]-phenylacrylate-ZA1963 urine contained more than 20 metabolites, including single phenyl ring metabolites 18 (isochromen-3-one), 55 ((E)-2-[2-(hydroxymethyl)phenyl]-3-methoxyacrylic acid), 56 (methyl (E)-2-[2-(glucuronidylmethyl)phenyl]-3-methoxyacrylate), and 58 (n (sulfooxy)iso-chromanone) that represented 23.26% of administered dose (all urinary metabolites were minor, with just the co-chromatographing metabolites 2 ((E)-2-{2-[6-(trifluoromethyl)pyridin-2-yloxymethyl]phenyl}-3-methoxyacrylic acid) and 48 (methyl 2,3-dihydroxy-2-[6-(trifluoromethyl)pyridin-2-yloxymethyl]phenyl}propionate) together exceeding 5% of administered dose. After the [^{14}C]-pyridinyl-ZA1963 dose, male urine contained (at 4.54% of dose)

the single pyridinyl ring metabolites 3 (6-(trifluoromethyl)pyridin-2-ol) at 0.32% of dose; 38 (2-glucuronidyl-6-(trifluoromethyl)pyridine) at 0.41% of dose; and 39 (2-sulphooxy-6-(trifluoromethyl)pyridine) at 2.33% of dose with minor proportions of metabolites 31 (2-oxo-{2-6-[trifluoromethyl)pyridin-2-yloxymethyl]phenyl}acetic acid), 44, 51, and unknown G. After the [^{14}C]-pyridinyl-ZA1963 dose, female urine contained (at 16.5% of dose) an array of minor metabolites including the single pyridinyl ring metabolites 3 and 38. The much lower urinary excretion level that resulted in bile duct cannulated males vs females and vs the relative equal urinary excretion levels between the non-cannulated sexes were seen as an indication that enterohepatic recirculation may be uniquely required for production of the majority of male urinary metabolites, since reabsorption of any biliary metabolites of ZA1963 in cannulated males was precluded by the total removal of bile.

In the [^{14}C]-phenylacrylate-ZA1963 low dose study (record 256744) (single dose at 10 mg/kg), 78% (males) and 61% (females) of administered radiolabel was excreted in feces with 21% (males) and 34% (female) of dose eliminated in urine during 120 hours. Metabolites in male and female fecal extracts were similar. The major fecal metabolite, metabolite 2 ((E)-2-{2-[6-trifluoromethyl) pyridin-2-yloxymethyl] phenyl}-3-methoxyacrylic acid), accounted for 16.78% (males) and 23.28% (females) of dose; the parent compound (ZA1963) for 9.49% (males) and 4.49% (females) of dose; metabolite 42 (methyl (E)-2-{4-hydroxy-2-[6-(trifluoromethyl)pyrindie-2-yloxymethyl]phenyl}-3-methoxyacrylate) for 11.4% (males) and 8.18% (females); metabolite 32 (methyl 3-hydroxy-2-{2-[6-(trifluoromethyl)pyridin-2-yloxymethyl]phenyl}propionate) for 7.84% (males) and 4.27% (females); and metabolite A (unidentified) for 10.54% (males) and 5.91% (females) of dose. All other fecal metabolites accounted for less than 5% of dose. Urinary metabolite profiles showed differences between the sexes. Urine from females contained 2 metabolites that exceeded 5% of administered dose, metabolite 52 (methyl 2-hydroxy-3-sulphooxy-2-{2-[6-(trifluoromethyl)pyridin-2-yloxymethyl]phenyl}propionate) at 6.47% of dose and 54 (N-carboxymethyl 2-{2-[6-(trifluoromethyl)pyridin-2-yloxymethyl]phenyl}acetamide) at 8.89% of dose (both were absent in male urine). In male urine, only the co-eluting metabolites 31 (2-oxo-{2-6-[trifluoromethyl)pyridin-2-yloxymethyl]phenyl}acetic acid) and 44 at 5.55% of dose were present (metabolite 44 was also seen in female urine at less than 2% of dose). Minor metabolites 18, 56, and 58 were common to urine from both sexes at less than 2%.

In the [^{14}C]-phenylacrylate-ZA1963 high dose study (record 256745) (single dose at 100 mg/kg), group means of 74% (males) and 65% (females) of administered radiolabel were excreted in feces with 18% (males) and 26% (females) of dose eliminated in urine during 120 hours. Chromatographic traces of radiolabeled metabolites, similar to the parent compound, accounted for 17.88% (males) and 19.22% (females) of the dose in fecal extracts; metabolite 2 for 10.89% (males) and 17.07% (females) of dose; metabolite 42 for 10.19% (males) and 9.73% (females) of dose; metabolite 32 for 6.68% (males) and 5.14% (females) of dose; metabolite 44 for 7.12% (males) of dose (it was absent in female fecal extracts); and metabolite A for 5.19 % (males) and 3.84% (females) of dose. Female urine contained just 1 metabolite (40 (glucuronidyl (E)-3-methoxy-2-{2-[6-(trifluoromethyl)pyridine-2-yloxymethyl]phenyl}acrylate)) (at 5.07%) that exceeded 5% of dose (it was not present in male urine). All other urinary metabolites accounted for less than 5% of dose, including metabolites 51, 55, 56, 57 (2-{n-hydroxy-2-[6-(trifluoromethyl)pyridin-2-yloxymethyl phenyl}malonic acid), and 58 which were common to both sexes.

In the [^{14}C]-phenylacrylate-ZA1963 repeat dose study (record 256746) (single dose at 10 mg/kg following 14 consecutive daily doses of unlabeled ZA1963), group means of 74% (males) and 65% (females) of administered radiolabel were excreted in feces with 18% (males) and 26% (female) of dose eliminated in urine during 120 hours. Metabolite 2 represented group mean values of 14.31% (males) and 26.48% (females) of administered dose in fecal extracts; unchanged ZA1963 was 10.73% (males) and 5.05% (females) of dose; metabolite 42 accounted for 10.33% (males) and 5.64% (females) of radiolabel; metabolite 32 was 6.54% (males) 8.27% (females) of dose; metabolite 44 was 8.42% (males) and 2.72% (females) of dose; and metabolite A represented 7.03% (males) and 4.54% (females) of radiolabel. Female urine contained 2

metabolites that exceeded 5% of administered radiolabel (metabolites 40 and 52 at group mean values of 7.36% and 6.13% of dose, respectively) (both were absent in male profiles). Metabolite 44 coeluted with 41 (44 was not present alone) together represented 3.45% of dose and was not present in male urine. Minor metabolites 18, 50 (or 50 and 54 coeluted), 56, and 58 were present in urine of both sexes at less than 3% of dose.

Overall, 42 metabolites were indicated and 34 of those were structurally identified. All metabolites that represented more than 5% of the administered dose were identified (with the exception of one (fecal metabolite A), however, it was considered to have originated from bile where all significant metabolites were identified). A proposed metabolic pathway for ZA1963 in the rat was provided (Figure 2 (page 80)). The major route of metabolism included O-demethylation, ester hydrolysis, ring separation and hydroxylation, which was consistent between the sexes following both single (10 and 100 mg/kg) and repeated doses (10 mg/kg).
Acceptable. (Green, 8/22/11).

**53149-0139 256744, "ZA1963: Excretion and Tissue Distribution of a Single Oral Dose (10 mg/kg) in the Rat", (A. Brown, Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK., Report No. CTL/P/5904, 17 September 1998). Five Alpk:AP$_f$SD rats per sex received a single oral gavage dose of [^{14}C]-phenylacrylate-ZA1963 at 10 mg/kg. The excretion of radioactivity in urine and feces was monitored (liquid scintillation counting (LSC)) for 120 hours post dosing (urine and feces were collected at 6 (urine only), 12, 24, 36, and 48 hours post-dosing and every 24 hours, thereafter). The animals were then sacrificed and residual radioactivity was measured (LSC) in blood (whole blood and plasma), carcass, brain, liver, lungs, gastrointestinal tract and contents, heart, spleen, kidneys, testes, ovaries, fat (abdominal), bone (femur), and muscle (femoral). Fecal excretion accounted for group mean values of 78% (males) and 61% (females) of administered dose during 120 hours (the majority was excreted during the 12 to 24 hour interval, 39% (males) and 30% (females)). Twenty-one % (males) and 34% (females) of administered radiolabel was excreted in urine during 120 hours post dosing. At termination, all tissue concentrations were < 0.1 μg equiv/g, except in G.I. tract (0.113 μg equiv/g for males and 0.216 μg equiv/g for females), kidneys (0.198 μg equiv/g for males and 0.184 μg equiv/g for females), liver (0.400 μg equiv/g for males and 0.248 μg equiv/g for females), blood (0.129 μg equiv/g for males and 0.127 μg equiv/g for females) and bone (0.104 μg equiv/g for males and 0.077 μg equiv/g for females). Group mean total administered radiolabel recovered in tissues and residual carcass was 0.76% (males) and 0.87% (females). Acceptable. (Green, 8/15/11). No worksheet.

**53149-0140 256745, "ZA1963: Excretion and Tissue Distribution of a Single Oral Dose (100 mg/kg) in the Rat", (A. Brown, Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK., Report No. CTL/P/5905, 17 September 1998). Five Alpk:AP$_f$SD rats per sex received a single oral gavage dose of [^{14}C]-phenylacrylate-ZA1963 at 100 mg/kg. Urine and feces were collected at 6 (urine only), 12, 24, 36, and 48 hours post dosing and every 24 hours, thereafter, to measure (LSC) the excretion of administered radiolabel. At the end of the 120 hour collection period, the animals were sacrificed and residual radioactivity in blood (whole blood and plasma), carcass, brain, liver, lungs, gastrointestinal tract and contents, heart, spleen, kidneys, testes, ovaries, fat (abdominal), bone (femur), and muscle (femoral) was determined (LSC). Group mean values of 74% (males) and 65% (females) of administered radiolabel were excreted in feces and 18% (males) and 26% (females) in urine during 120 hours. Maximum excretion occurred in the 12 to 24 hour interval (28% (males) and 19% (females) of dose in feces and 6% (males) and 8% (females) in urine. Group mean tissue concentrations were 1.645 μg equiv/g (males) and 2.990 μg equiv/g (females) in the G.I. tract, 1.907 μg equiv/g (males) and 2.329 μg equiv/g (females) in kidneys, 3.756 μg equiv/g (males) and 3.056 μg equiv/g (females) in liver, 1.497 μg equiv/g (males) and 1.837 μg equiv/g (females) in blood, and 1.115 μg equiv/g (males) and 1.238 μg equiv/g (females) in plasma (all other tissue concentrations were less than 0.65 μg equiv/g (males) and 0.85 μg equiv/g (females)). Group mean total administered radioactivity present in tissues and residual carcass was 0.78%

(males) and 0.91% (females). Acceptable. (Green, 8/16/11). No worksheet.

**53149-0141 256746, "ZA1963: Excretion and Tissue Distribution of a Single Oral Dose (10 mg/kg) in the Rat Following Repeat Dosing", (A. Brown, Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK., Report No. CTL/P/5906, 22 September 1998). Seven Alpk:AP_fSD rats per sex received 14 consecutive daily oral gavage doses of unlabeled ZA1963 (picoxystrobin technical) (99.8%) at 10 mg/kg. Twenty-four hours after the last unlabeled dose, 5 rats per sex received a single oral gavage dose of [^{14}C]-phenylacrylate-ZA1963 at 10 mg/kg. After the radiolabeled dose, urine and feces were collected at 6 (urine only), 12, 24, 36, and 48 hours, and at 24 hour intervals, thereafter, to 120 hours. After the 120 hour collection period, the animals were sacrificed and residual radioactivity in blood (whole blood and plasma), carcass, brain, liver, lungs, gastrointestinal tract and contents, heart, spleen, kidneys, testes, ovaries, fat (abdominal), bone (femur), and muscle (femoral) was determined (LSC). The primary route of radiolabel excretion was in feces with group mean values of 77% (males) and 63% (females). Group mean values excreted in urine during 120 hours were 19% (males) and 32% (females). Maximum excretion in feces was noted at the 12 to 24 hour interval in males (46%) and females (30%). Urinary elimination of radiolabel peaked in the 6 to 12 hour interval in males (6%) and in the 12 to 24 hour interval for females (9%). Group mean tissue concentrations were 0.120 μg equiv/g (males) and 0.251 μg equiv/g (females) in the G.I. tract, 0.206 μg equiv/g (males) and 0.187 μg equiv/g (females) in kidneys, 0.470 μg equiv/g (males) and 0.258 μg equiv/g (females) in liver, 0.142 μg equiv/g (males) and 0.133 (females) in blood, and 0.100 μg equiv/g (males) and 0.096 μg equiv/g (females) in plasma (concentrations in all other tissues were < 0.1 μg equiv/g). Group mean recovery of administered radiolabel from tissues and residual carcass was 0.72% (males) and 0.77% (females). Acceptable. (Green, 8/16/11). No worksheet.

53149-0137 256739, "^{14}C-Picoxystrobin (DPX-YT669): Plasma and Red Blood Cell Pharmacokinetics and Tissue Distribution in Male and Female Rats", (M.W. Himmelstein, E.I. du Pont de Nemours and Company, DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE., USA, Laboratory Project ID: DuPont-26451, 1 March 2010). Four Crl:CD(SD) rats per sex per group with jugular vein cannulas received a single oral gavage dose of [Phenyl(U)-^{14}C]-Picoxystrobin or [Pyridine-3-^{14}C]-Picoxystrobin at 10 or 100 mg/kg. Whole blood was collected at 0, 15, 30 minutes and 1, 2, 4, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours post treatment and the plasma was separated from erythrocytes (centrifugation). Erythrocytes were analyzed (liquid scintillation counting (LSC)) to determine total radioactivity present. The concentration time course data for plasma from each animal were analyzed (LSC) to determine the elimination half-life (T1/2), area-under-the-curve extrapolated to infinity (AUCINF), peak and half peak concentrations (Cmax and Cmax/2), and time to peak and half peak concentrations (Tmax and Tmax/2). Urine and feces were collected (on dry ice) pre-dose, 0 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, 120 to 144, and 144 to 168 hours after dosing and stored frozen for potential future metabolite profiling. After a 100 mg/kg dose of [Pyridine-3-^{14}C]-Picoxystrobin, one male and 1 female were found dead at 120 hours post-dosing and1 female died within an hour after dosing (animals were not replaced). One female that received [Phenyl(U)-^{14}C]-Picoxystrobin at 100 mg/kg died within 1 hour of dosing and was replaced. After a phenyl(U)-^{14}C]-picoxystrobin dose, group mean values in plasma included: T1/2 values of 47.2 hours (males) and 40.2 hours (females) at 10 mg/kg and 37.2 hours (males) and 30.5 hours (females) at 100 mg/kg; Cmax values of 4.8 μg equivalent/g at 10 mg/kg and 12.4 μg equivalent/g at 100 mg/kg for males and 2.8 μg equivalent/g at 10 mg/kg and 18.2 μg equivalent/g at 100 mg/kg for females; Tmax values of 2.2 hours (males) and 7.1 hours (females) at 10 mg/kg and 12.3 hours (males) and 9.3 hours (females) at 100 mg/kg; and AUCINF values (hr*μg/g) of 110.2 (males) and 85.9 (females) at 10 mg/kg and 605.0 (males) and 709.6 (females) at 100 mg/kg. Following the [pyridine-3-^{14}C]-picoxystrobin dose, resulting group mean values were: T1/2 values of 33.4 hours (males) and 34.1 hours (females) at 10 mg/kg and 45.8 hours (males) and 32.9 hours (females) at 100 mg/kg; Cmax values (μg equivalent/g) of 3.4 (males) and 4.5 (females) at 10 mg/kg and 14.8 (males) and 11.4 (females)

at 100 mg/kg; Tmax values of 3.0 hours (males) and 0.6 hours (females) at 10 mg/kg and 12.2 hours (both sexes) at 100 mg/kg; and AUCINF values of 101.8 hr*μg/g (males) and 86.7 hr*μg/g (females) at 10 mg/kg and 579.3 hr*μg/g (males) and 453.4 hr*μg/g (females) at 100 mg/kg. Supplemental data. (Green, 8/30/11).

53149-0142 256747, "ZA1963: Whole Body Autoradiography in the Rat", (D.J. Davies, Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK., Report No. CTL/P/5646, 29 October 1997). One Alpk:AP_fSD rat per sex received a single oral gavage dose of [^{14}C]-phenyl ZA1963 or [^{14}C]-pyridyl ZA1963 at 10 mg/kg. After dosing, urine (along with cage wash) and feces were collected at 6 (urine and cage wash only), 12 and 24 hours post treatment and analyzed for radiolabel (liquid scintillation counting (LSC)). The exhaled air of each animal was trapped and analyzed (LSC) for volatile metabolites at 12 and 24 hours post treatment. Animals excreted 21.0% (male) and 25.0% (female) of administered radiolabel in urine and 13.4% (male) and 19.1% (female) of dose in feces during 24 hours after a single oral gavage dose of [^{14}C]-pyridyl-ZA1963 at 10 mg/kg (less than 0.4% of dose was exhaled as volatile metabolites) and 17.8% (male) and 30.2% (female) of administered dose in urine and 19.6% (male and female) of dose in feces and less than 0.1% of dose as volatiles during 24 hours after the [^{14}C]-phenyl ZA1963 dose. Whole body autoradiograms showed no marked differences in the distribution of radioactivity between males and females dosed with either radiolabeled form of ZA1963. In all rats , the greatest intensity of labeling was present in the intestinal tract contents, followed by the liver and then the kidneys. A low intensity of radiolabel was noted in blood and low levels were evident in many tissues, including heart, lungs, and nasal passages. Supplemental data. (Green, 8/24/11).

NEUROTOXICITY STUDIES

Rat Acute Oral Neurotoxicity Study

**53149-0135 256737, "Picoxystrobin (DPX-YT669) Technical: Acute Oral Neurotoxicity Study in Rats", (L.A. Malley, E.I. du Pont de Nemours and Company, DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE., Laboratory Project ID. DuPont-27313, 25 February 2010). Twelve Crl:CD(SD) rats per sex per group received a single oral gavage dose of DPX-YT669 (picoxystrobin technical) (99.3%) at 0 (0.5% methylcellulose at 10 ml/kg), 200, 1000, and 2000 mg/kg followed by a 14 day observation period. On test day one, 2 high dose females were found dead and another was sacrificed in moribund condition. All high dose males survived to scheduled termination. The incidence of diarrhea was increased for mid and high dose males (test days 2 to 4) and for high dose females (test day 1). Group mean bodyweight gain was reduced at study days 1 to 2 for both sexes at 200 mg/kg and higher vs controls (statistically significant for males at all dose levels and for high dose females). Additionally, group mean food consumption was significantly reduced in both sexes at all treated levels for days 1 to 2 vs controls. No significant decreases in group mean bodyweight or bodyweight gain, or group mean food consumption were recorded at 200 mg/kg and higher for days 2 to 8, 8 to 15, or 1 to 15 compared to controls. Group mean body temperature was significantly reduced on test day 1 in females at 200 mg/kg and above and in males at 1000 mg/kg and higher vs controls (note that group mean control body temperatures were lower (ns) than pretreatment baseline values on test day 1). Body temperatures for all treated animals were comparable to control values on the test days 8 and 15 evaluations. Additionally, the mean number of rearing movements was significantly lower on test day 1 for females at 200 and above, and for 2000 mg/kg males. Rearing movements in all treated groups were comparable to control values at test days 8 and 15. In the home cage on test day 1, significant increases in ptosis were noted for males and females at 1000 mg/kg and above along with increases in curled up posture in males compared to controls. In the open field on test day 1, increased incidences of ptosis were noted for males at 1000 and 2000 mg/kg (statistically significant at 2000 mg/kg) vs controls. Additionally, increased incidences of low arousal were recorded for

200 mg/kg and above males and for 1000 mg/kg and above females vs controls (statistical significance was attained for high dose males only). Also, in high dose females, significantly increased incidences of abnormal posture (high carriage) and uncoordinated gait were noted vs controls (non significant increases were noted in muscle fasciculations for high dose females and in abnormal posture for mid dose females). Significantly increased incidences of diarrhea were recorded for mid and high dose males (motor activity monitoring and open field) and in high dose females (open field) vs controls. Treatment-related decreases in motor activity (MA) were observed in 200 mg/kg and above males and females. On test day 1, mean duration of movement was significantly lower for 200 mg/kg and above males and/or females during the first 3 ten-minute intervals, and during the fourth 10-minute interval for high dose animals vs controls. Additionally, the mean number of movements was significantly decreased for high dose males (at the first 3 ten-minute intervals) and females (at the first 2 ten-minute intervals) and for low and mid dose males (at the second and third 10-minute intervals) on day 1. No treatment-related MA effects were indicated on test days 8 and 15 in males and females at any treatment level. Gross pathology was unremarkable. No treatment-related neuropathology changes were indicated. Systemic NOEL < 200 mg/kg (reduced bodyweight gain and food consumption at all dose levels for test days 1 to 2, FOB (low arousal) and MA day 1 changes). No adverse effect. Acceptable. (Green, 5/16/11).

Rat 90-Day Dietary Neurotoxicity Study

**53149-0134, 0136 256736, 256738, “Picoxystrobin (DPX-YT669) Technical: Subchronic Neurotoxicity 90-Day Feeding Study in Rats”, (S.S. Anand, E.I. du Pont de Nemours and Company, DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE., Laboratory Project ID. DuPont-27312, 9 February 2010). Twelve Crl:CD(SD) rats per sex per group received DPX-YT669 (picoxystrobin technical) (99.3%) in the diet at 0 (basal diet), 100, 600, and 3500 ppm for up to 14 weeks. Group mean daily intake of DPX-YT669 during the study was 6, 36, and 207 mg/kg/day for males and 8, 46, and 246 mg/kg/day for females at 100, 600, and 3500 ppm, respectively. All animals survived to the end of the treatment period and no treatment-related clinical signs were indicated. Group mean bodyweight and bodyweight gain were significantly reduced for high dose males and females during the study. Final (day 91) group mean bodyweight was 77% (males) and 85% (females) of control values and overall (days 0 to 91) group mean bodyweight gain was 62% (males) and 69% (females) of controls. In females at 100 and 600 ppm, non-statistically significant reductions in group mean final bodyweight (95% and 92% of control values, respectively) and overall group mean bodyweight gain (91% and 86% of controls, respectively) were recorded (note that significant reductions in group mean bodyweight gain were recorded for 600 ppm females for days 0 to 28 (80% of controls) and that bodyweight gains during days 28 to 56 and 56 to 91 were comparable to controls, but insufficient to compensate for the earlier reductions). At 3500 ppm, overall group mean food consumption (days 0 to 91) was significantly reduced for males (22%) and females (18%) vs controls. In females at 100 and 600 ppm, overall group mean food consumption was 96% and 93% of control values, respectively (ns) (statistically significant decreases were noted at 600 ppm for test days 0 to 28 and 42 to 49). Significant reductions in forelimb and hindlimb grip strength were noted in 3500 ppm males during the week 8 evaluation and in forelimb grip strength during week 13 compared to controls (values were reported to be within the historical control range at the performing laboratory). No treatment-related grip strength changes were noted for females at any level. No other treatment related FOB effects were noted. No treatment related effects were indicated for motor activity (MA) (number and duration of movements) at any treatment level in either sex. No treatment-related neuropathology changes were indicated. Record 256738 is a positive control rat neurotoxicity study with carbaryl (performed in 2008) submitted to validate study procedures at the performing laboratory. Systemic NOEL = 600 ppm (36 mg/kg/day (males) and 46 mg/kg/day (females)) based on reduced bodyweight and food consumption. Neurotoxicity NOEL = 3500 ppm (207 mg/kg/day (males) and 246 mg/kg/day (females)). No adverse effect. Acceptable. (Green, 5/11/11).

IMMUNOTOXICITY STUDIES

Rat 28-Day Dietary Immunotoxicity Study

**53149-0145 256750, "Picoxystrobin (DPX-YT699) Technical: 28-Day Immunotoxicity Feeding Study in Rats", (D. Hoban, E.I. du Pont de Nemours and Company, DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE., Laboratory Project ID. DuPont-27310, 1 March 2010). Ten Crl:CD(SD) rats per sex per group received DPX-YT669 (picoxystrobin technical) (99.3%) in the diet at 0 (basal diet), 50, 200, 1000, and 3500 ppm for 28 days. All animals were injected intravenously (IV) (lateral tail vein) with 0.5 ml of 4 x 10^8 sheep red blood cells (sRBC)/ml on test day 23. Animals were sacrificed on test day 28 and 4 ml of blood were collected (abdominal *vena cava*) from each animal for humoral immune function. Sera samples (including positive control serum) were evaluated using sRBC specific IgM levels with an enzyme-linked immunosorbent assay (ELISA). Group mean overall test article intake was calculated to be 3.5, 15, 68, and 231 mg/kg/day for males and 3.9, 16, 75, and 229 mg/kg/day for females at 50, 200, 1000, and 3500 ppm, respectively. All animals survived to scheduled sacrifice with no treatment-related clinical signs reported at any dose level. At 3500 ppm, significant reductions were noted in group mean bodyweight for males on test days 7, 14, 21, and 28 and for females on test days 7, 14, and 28 and in group mean bodyweight gains for both sexes during test days 0 to 7 and 0 to 28 vs controls. Significant reductions in group mean food consumption were noted at the high dose level in males (days 0 to 7 and 0 to 28) and females (days 0 to 7, 7 to 14, 14 to 21, 21 to 28, and 0 to 28) vs controls. No treatment-related effects were noted for absolute or relative brain, spleen, and thymus weights. Necropsy results were unremarkable. No treatment-related effects on the primary humoral immune response were noted for either sex at any diet concentration vs controls. The positive control was functional. No immunotoxicity, no adverse effect. Immunotoxicity NOEL = 3500 ppm (231 mg/kg/day for males and 229 mg/kg/day for females). Systemic NOEL = 1000 ppm (68 mg/kg/day for males and 75 mg/kg/day for females) based on reduced bodyweight, bodyweight gain, and food consumption. Acceptable. (Green, 5/17/11).

Mouse 4-Week Dietary Immunotoxicity Study

**53149-0146 256751, "Picoxystrobin (DPX-YT669) Technical: 28-Day Immunotoxicity Feeding Study in Mice", (D. Hoban, E.I. du Pont de Nemours and Company, DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE., Laboratory Project ID. DuPont-27311, 1 March 2010). Ten Crl:CD1(ICR) mice per sex per group received DPX-YT669 (picoxystrobin technical) (99.3%) in the diet at 0 (basal diet), 100, 600, 2400, and 4800 ppm for 28 days. On test day 23, all animals were injected intravenously (lateral tail vein) with 0.2 ml of 5 x 10^8 sheep red blood cells (sRBC)/ml. Animals were sacrificed on test day 28 and 1 ml of blood was collected (abdominal *vena cava*) from each animal for humoral immune function. Sera samples (including positive control serum) were evaluated using sRBC specific IgM levels with an enzyme-linked immunosorbent assay (ELISA). Group mean overall test article intake was calculated to be 16, 95, 358, and 727 mg/kg/day for males and 20, 127, 449, and 931 mg/kg/day for females at 100, 600, 2400, and 4800 ppm, respectively. All animals survived to scheduled sacrifice. There were no treatment related changes in clinical signs, food consumption, or bodyweight at any dietary concentration. No treatment-related effects were noted for absolute or relative brain, spleen, and thymus weights. Necropsy results were unremarkable. No treatment-related effects were noted for the primary humoral immune response in either sex at any diet concentration vs controls. No adverse effect. The positive control was functional. Systemic and Immunotoxicity NOEL = 4800 ppm (727 mg/kg/day for males and 931 mg/kg/day for females). Acceptable. (Green, 8/10/11).