

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Cyantraniliprole

Chemical Code # 6072, Tolerance # 53160
SB 950 # NA

Original: 4/27/12

Revised: 8/6/12

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, possible adverse effect
Oncogenicity, rat:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, 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 ¹

Toxicology one-liners are attached.

All record numbers through #265212 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T120806

Revised by T. Moore, 4/27/12, H. Green, 8/6/12

¹Acceptable acute and subchronic rat neurotoxicity studies have been submitted. A delayed neurotoxicity study in hens is not required at this time.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

COMBINED, RAT

** 53160-0398; 260630; "Cyantraniliprole Technical (DPX-HGW86 Commercial Batch-412): Combined Chronic Toxicity/Oncogenicity Study, 2-Year Feeding Study in Rats"; (L. Craig; MPI Research, Inc., Mattawan, MI; Study No. 125-101; 4/28/11); Sixty Sprague-Dawley rats/sex/group received 0, 20, 200, 2000 or 20000 ppm of Cyantraniliprole (DPX-HGW86) Technical (lot no. DPX-HGW86-412; purity: 97.0%) in the diet for 2 years ((M) 0, 0.81, 8.31, 84.8, 907 mg/kg/day, (F) 0, 1.09, 10.5, 106.6, 1161 mg/kg/day). An additional chronic cohort of 10 animals/sex/group received the test material in the diet for one year ((M) 0, 0.92, 9.34, 94.1, 996 mg/kg/day, (F) 0, 1.17, 11.6, 117.1, 1248 mg/kg/day). Survival of the study animals was not affected by the treatment. The mean body weight gain of both sexes in the 2000 and 20000 ppm groups was less than that of the control group through the first 13 weeks of treatment (NS, $p < 0.05$). Thereafter the effect was not so apparent. The mean food consumption was not apparently affected by the treatment. There was no apparent treatment-related effect upon food consumption. The ophthalmological examination did not reveal any treatment-related effects. There was no treatment-related effect noted in the hematological evaluation and urinalysis. In the clinical chemistry, minor increases were noted for the mean serum gamma glutamyl transferase, aspartate aminotransferase and alanine aminotransferase activity levels of the 20000 ppm males, but these did not constitute a frank treatment-related effect on the liver. The mean absolute and relative liver weights of both sexes in the 2000 and 20000 ppm groups were greater than the control values at both the 12-month and 24-month evaluations (NS, $p < 0.05$ or 0.01). In the histopathology, hepatocytic centrilobular hypertrophy was noted in the livers of both sexes after 12 months of treatment ((M) 0: 0/10 vs. 2000: 5/10 and 20000: 8/10, (F) 0: 0/10 vs. 2000: 4/10 and 20000: 6/10). At 24 months, both sexes in the 20000 ppm group and the females in the 2000 ppm group demonstrated this effect ((M) 0: 0/60 vs. 20000: 6/60, (F) 0: 0/60 vs. 2000: 9/60 and 20000: 22/60). Other effects noted in the livers of the males were basophilic foci of alteration and focal vacuolation. Although there was a dose-related increase in the incidences of these effects, the background incidence in the control group was quite high and did not constitute a treatment-related effect. An apparent dose-related increase in the incidence of chronic progressive nephropathy was noted in the females after 24 months of treatment. The incidence of this effect was also high in the control group and was not evident after 12 months of treatment. There was no treatment-related increase in the incidence of tumors. **No adverse effect indicated. Rat Chronic Dietary Toxicity NOEL:** (MF) 200 ppm ((M) 9.34 mg/kg/day, (F) 11.6 mg/kg/day) (based on the hepatocytic hypertrophy of the liver of both sexes in the 2000 ppm treatment group). **No oncogenicity was evident. Study acceptable.** (Moore, 12/2/11)

CHRONIC TOXICITY, RAT

See Combined Rat above.

CHRONIC TOXICITY, DOG

** 53160-0344, -0423; 260567, 260659; "DPX-HGW86 Technical: Chronic Toxicity 1-Year Feeding Study in Dogs"; (E.M. Luckett; MPI Research, Inc., Mattawan, MI and E.I. du Pont de Nemours & Co., DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE; Study No. 125-056 (Project ID. No. DuPont-19180); Four beagle dogs/sex/group received 0, 40, 200, 1000, 5000 ppm of DPX-HGW86 Technical (batch no. DPX-HGW86-230; purity: 94.5%) in the diet for 52 weeks ((M): 0, 0.96, 5.7, 27.0, 143.8 mg/kg/day, (F) 0, 1.12, 6.0, 27.1, 133.0 mg/kg/day). An additional 3 animals/sex were included in the 5000 ppm group and received the treatment for 12 weeks. Thereafter they were maintained as a recovery cohort until the termination of the study. One male in the 5000 ppm group was euthanized *in extremis* on day 80 (one of the males in the

recovery cohort was substituted and maintained on the treatment regimen throughout the remainder of the study). The cause of death was attributed to Canine Juvenile Polyarteritis Syndrome (CJPS). Other dogs were possibly suffering CJPS as well. One female in the 5000 ppm group was euthanized on day 176. She was noted to be suffering from septicemia. The mean body weight gain of both sexes in the 5000 ppm group was less than that of the control group over the course of the study (NS). The mean food consumption was not affected by the treatment. There were no apparent treatment-related clinical signs. The ophthalmological examination, hematological evaluation, and urinalysis did not reveal any apparent treatment-related effects. In the clinical chemistry evaluation, the serum alkaline phosphatase activity levels were elevated for both sexes in the 200 ppm group and above and for the males in the 40 ppm group in a dose-related manner (NS, $p < 0.05$ or 0.01). The alanine aminotransferase activity was elevated in the serum of both sexes in the 1000 and 5000 ppm groups (NS, $p < 0.05$ or 0.01). The serum albumin concentrations of both sexes in the 1000 and 5000 ppm groups were less than those of the control group throughout the study ($p < 0.05$ or 0.01). The serum cholesterol levels of both sexes in the 1000 and 5000 ppm groups were lower than the control group values throughout the treatment period (NS, $p < 0.05$). Analysis of the plasma for the presence of the parent compound and/or any metabolites during week 39 in the 5000 ppm cohorts (both treated and recovery) revealed only the presence of the parent compound (treated cohort: (M) 62,200 ng/ml, (F) 56500 ng/ml; recovery cohort: (M) 19.7 ng/ml, (F) 10.8 ng/ml). The mean absolute and relative liver weights were increased in a dose-related manner for both sexes in the 200 ppm treatment group and above and for the males in the 40 ppm group (NS, $p < 0.05$ or 0.01). The mean absolute and relative thyroid weights of the 5000 ppm males were greater than the control group values ($p < 0.05$ or 0.01). In the histopathology, hepatocellular degeneration was noted in the liver of both sexes in the 1000 ppm and 5000 ppm groups ((M) 0: 0/4 vs. 1000: 3/4, 5000: 4/4, (F) 0: 0/4 vs. 1000: 4/4, 5000: 3/3). Tubular vacuolation was evident in the kidneys of the 5000 ppm males (0: 1/4 vs. 5000: 4/4). Tubular vacuolation was noted in 3 of 4 kidneys in the control and 3 of 3 kidneys in the 5000 ppm females. No residual treatment-related effects were noted for the animals in the recovery cohort. **Possible adverse effect:** hepatocellular degeneration; **Dog Subchronic Dietary Toxicity NOEL:** (M) < 40 ppm ((M) < 0.96 mg/kg/day) (based upon increased levels of serum alkaline phosphatase activity and increased liver weights noted for males in the 40 ppm group) ((F) 1.12 mg/kg/day) (based upon increased levels of serum alkaline phosphatase activity and increased liver weights noted for females in the 200 ppm group); **Study acceptable.** (Moore, 10/31/11)

ONCOGENICITY, RAT

See Combined Rat above.

ONCOGENICITY, MOUSE

** 53160-0399; 260633; "Cyantraniliprole Technical (DPX-HGW86 Commercial Batch-412): Oncogenicity Study, 18-Month Feeding Study in Mice"; (L. Craig; MPI Research, Inc., Mattawan, MI; Study No. 125-100; 4/26/2011); Sixty CD-1 mice/sex/group received 0, 20, 150, 1000 or 7000 ppm of Cyantraniliprole (DPX-HGW86) Technical (lot no. DPX-HGW86-412; purity: 97.0%) in the diet for 18 months ((M) 0, 2.03, 15.45, 103.6, 768.8 mg/kg/day; (F) 0, 2.44, 18.57, 131.0, 903.8 mg/kg/day). There was no treatment-related effect upon the survival of the study animals. The mean body weight gains of both sexes in the 7000 ppm group were less than those of the control group after 13 weeks of treatment and of the males in the 7000 ppm group after 1 year of treatment ($p < 0.05$ or 0.01). There was no apparent treatment-related effect upon food consumption. No treatment related effects were noted in the ophthalmological examination. In the hematology evaluation, there was no treatment-related effect upon the differential leucocyte counts after 18 months of treatment. The mean absolute and relative liver weights of both sexes in the 1000 and 7000 ppm groups were greater than the control group values (NS, $p < 0.05$ or 0.01). In the

histopathological examination, an increased incidence hepatocytic centrilobular hypertrophy was noted in the livers of both sexes in the 1000 and 7000 ppm groups ((M) 0: 3/60 vs. 1000: 13/60, 7000: 36/60); (F) 0: 0/59 vs. 1000: 5/60, 7000: 9/60). **No adverse effects indicated. Mouse Chronic Toxicity NOEL:** (M/F) 150 ppm ((M) 15.45 mg/kg/day, (F) 18.57 mg/kg/day) (based upon the increased incidence of hepatocytic centrilobular hypertrophy in the livers of both sexes in the 1000 ppm group); no oncogenicity evident; **Study acceptable.** (Moore, 12/7/11)

REPRODUCTION, RAT

** 53160-0346; 260569; "DPX-HGW86 Technical: Oral (Diet) Two-Generation (One Litter per Generation) Reproduction Toxicity Study in Rats"; (J.F. Barnett, Jr.; Charles River Laboratories, Preclinical Services, Horsham, PA; Study No. DuPont-19187; 4/21/11); Thirty Crl:CD(SD) rats/sex/group were dosed in the diet with 0, 20, 200, 2000 or 20000 ppm of DPX-HGW86 Technical (batch no. DPX-HGW86-230; purity: 94.5%) for two generations. The treatment period for the P parents included 70 days prior to mating, the mating period, 3 weeks of gestation and 3 weeks of lactation. At that time, 30 F1 animals/sex/group were selected as parents and treated for 70 days in the pre-mating period, the mating period, and 3 weeks for the gestation and lactation periods, respectively. None of the deaths of parental animals which occurred during the study were treatment-related. The mean body weights of both sexes in the 20000 ppm groups of both generations were less than the control values over the course of the treatment periods (NS, $p < 0.01$). There was no apparent treatment-related effect upon the food consumption. **In the P generation**, the mean absolute and relative liver weights of both sexes in the 20000 ppm group and the mean relative liver weight of the 2000 ppm males were greater than those of the control values ($p < 0.05$ or 0.01). The mean absolute and relative thyroid weights of both sexes in the 20000 ppm group and of the females in the 200 and 2000 ppm groups were greater than the control group values ($p < 0.01$). The mean absolute and relative thymus weights of the 2000 and 20000 ppm females were less than those values for the control group ($p < 0.01$). In the histopathology, hepatocellular hypertrophy was noted in the liver of both sexes in the 2000 and 20000 ppm group. An increased incidence of follicular cell hypertrophy in the thyroids of both sexes in the 2000 and 20000 ppm groups was evident. An increased incidence of vacuolation in the adrenal cortex of the 2000 and 20000 ppm males was noted. An increased incidence of thymic atrophy was evident for the 2000 and 20000 ppm females. **In the F1 generation**, the time to vaginal patency was delayed by approximately two days for the 20000 ppm females (control: 32.9 days vs. 20000: 35.1 days, $p < 0.01$). The mean relative liver weights of both sexes in the 2000 and 20000 ppm groups were greater than the control group values ($p < 0.01$). The mean absolute liver weights of the 2000 and 20000 ppm females were greater than the control value ($p < 0.01$). The mean absolute and relative thyroid weights of both sexes in the 20000 ppm group were greater than those of the control group ($p < 0.01$). The mean absolute and relative thymus weights of the 20000 ppm females were less than the control group values ($p < 0.01$). In the histopathology, hepatocellular hypertrophy was noted in the liver of both sexes in the 2000 and 20000 ppm group. An increased incidence of follicular cell hypertrophy in the thyroids of both sexes in the 200, 2000 and 20000 ppm groups was evident. An increased incidence of vacuolation in the adrenal cortex in all of the male treatment groups was noted. Thymic atrophy was noted for females in the 2000 and 20000 ppm group. There was no treatment-related effect upon any of the mating parameters or the size of the litters. There was no treatment-related effect upon the morphology or motility of the sperm in the males of either the P or F1 generations. Ovarian follicular counts of the F1 generation females were not affected by the treatment. The mean F2 pup weights for the 200 ppm group and above in both generations were less than those of the control by day 21 post-partum (NS or $p < 0.01$ or 0.05). Although the weaning index of the 20000 ppm group in the P generation was significantly less than that of the control group ($p < 0.01$), this effect was not apparent for the F1 generation. **No adverse reproductive effect indicated. Parental NOEL: (M)** < 20 ppm (< 1.7 mg/kg/day) (based upon the incidence of vacuolation in the cortex of the adrenal gland of the males in the 20 ppm group of the F1 generation)

(F) 20 ppm (1.4 mg/kg/day (based upon increased thyroid weights of the females in the P generation); **Reproductive NOEL: (M/F)** 20000 ppm ((M) 1910 mg/kg/day, (F) 2125 mg/kg/day) (based upon the lack of treatment-related effects on reproduction parameters of the 20000 ppm treatment group) **Developmental NOEL: (F)** 20 ppm (2.7 mg/kg/day) (based upon lower mean pup weights for the 200 ppm F2 pups during the lactation period); **Study acceptable.** (Moore, 11/7/11)

TERATOLOGY, RAT

** 53160-0347; 260570; "DPX-HGW86 Technical: Developmental Toxicity Study in Rats"; (S.M. Munley; E.I. du Pont de Nemours & Co., DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE; Project ID No. DuPont-19188; 4/17/09); Twenty two time-mated CrI:CD (SD) female rats/group were dosed orally by gavage with 0 (vehicle: aqueous 0.5% methylcellulose), 20, 100, 300 or 1000 mg/kg/day of DPX-HGW86 Technical (batch no. DPX-HGW86-230; purity: 94.5%) from day 6 of gestation through day 20. No maternal deaths resulted from the treatment. The mean body weight gains of the dams in the 100 mg/kg group and above were less than that of the control between day 6 and 7 of gestation ($p < 0.05$). The mean food consumption of the dams in the 300 and 1000 mg/kg groups was less than the control group between days 6 and 8 of gestation ($p < 0.05$). Thereafter, there was no treatment related effect on body weight gain or food consumption. There was no treatment-related effect upon any of the developmental parameters of the fetuses. **No adverse effect indicated. Maternal NOEL:** 20 mg/kg/day (based upon the reduced body weight gain noted for the dams in the 100 mg/kg treatment group at the initiation of dosing); **Developmental NOEL:** 1000 mg/kg/day (based upon the lack of treatment-related effect on the fetuses in the 1000 mg/kg treatment group); **Study acceptable.** (Moore, 11/9/11)

TERATOLOGY, RABBIT

** 53160-0348; 260571; "DPX-HGW86 Technical: Developmental Toxicity Study in Rabbits"; (S.M. Munley; E.I. du Pont de Nemours & Co., DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE; Project ID No. DuPont-19189; 6/12/09); Twenty two time-mated female Hra:(NZW)SPF rabbits/group were dosed orally by gavage with 0 (vehicle: aqueous 0.5% methylcellulose), 25, 100, 250 or 500 mg/kg/day with DPX-HGW86 Technical (batch no. DPX-HGW86-230; purity: 94.5%) from day 7 through day 28 of gestation. Two does in the 100 mg/kg group were euthanized *in extremis* on gestation days 15 and 24, respectively. Four does in the 250 mg/kg group and 3 does in the 500 mg/kg aborted or delivered early between days 22 and 29 after being observed suffering from diarrhea and loss of weight. One doe in both the control and the 500 mg/kg groups died as a consequence of an intubation error. The mean body weight gain for the does in the 250 and 500 mg/kg groups was less than that of the control animals over the course of the treatment ($p < 0.05$). The mean food consumption values of the 100 mg/kg group and above were less than the control group between gestation days 7 and 29 ($p < 0.05$). No treatment-related effect was noted on the development of the fetuses. **No adverse effect indicated. Maternal NOEL:** 25 mg/kg/day (based upon treatment-related effects on mean food consumption and the poor health of the does in the 100 mg/kg treatment group); **Developmental NOEL:** 500 mg/kg/day (based upon the lack of treatment-related effects upon the fetuses in the 500 mg/kg group); **Study acceptable.** (Moore, 11/10/11)

GENE MUTATION

** 0353, 260576; "IN-JSE: *In Vitro* Mammalian Cell Gene Mutation Test (CHO/HGPRT Assay)" (Clarke, J.J., BioReliance, Rockville, MD for E.I. du Pont de Nemours and Company, DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE, BioReliance Study Number AC22CC.782.BTL, 02/04/2009). 870.5300. Cultures of the Chinese hamster ovary (CHO-K-BH4) cell line (HGPRT locus) were treated with IN-JSE76 (a metabolite of cyantraniliprole, Lot (Dash) 005, purity = 93.8%), in the presence and absence of rat liver S-9 activation system, for 5 hours at concentrations of 0 (DMSO), 100, 150, 500, 1000, and 1500 ug/ml. Positive controls of ethyl methanesulphonate (EMS) (non-activated) and benzo(a)pyrene (B(a)P) (activated) were

used. No evidence of mutagenic effects was observed in this mammalian forward mutation system. **No adverse effects indicated. Acceptable.** (Corlett and Leung, 11/17/2011)

** 0358, 260581; "Cyantraniliprole (DPX-HGW86) Technical: Bacterial Reverse Mutation Assay" (Wagner, V.O. and VanDyke, M.R., BioReliance, Rockville, MD for E.I. du Pont de Nemours and Company, DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE, BioReliance Study Number AC25MV.503.BTL, 05/26/2009). 870.5100. Triplicate cultures of *S. typhimurium* strains TA1535, TA1537, TA98, and TA100 and of *Escherichia coli* WP2 *uvrA* were exposed (plate incorporation method) to cyantraniliprole (DPX-HGW86-425, batch/lot number 9182-3B, purity = 97.7%), in the presence and absence of S9 rat liver fraction, at 0 (DMSO), 50, 150, 500, 1500, and 5000 ug/plate and incubated for 48 to 72 hours at 37± 2°C. Positive controls were functional. There was no treatment-related increase in mutation frequency. Negative results indicate that under these test conditions the test article is not mutagenic in these tested species. **No adverse effects indicated. Acceptable.** (Corlett and Leung, 12/08/2011)

** 0408, 260644; "Cyantraniliprole (DPX-HGW86) Technical: Bacterial Reverse Mutation Assay" (Wagner, V.O. and Jois, M., BioReliance, Rockville, MD, BioReliance Study Number AD10PN.503.BTL, 11/29/2010). 870.5100. Triplicate cultures of *S. typhimurium* strains TA1535, TA1537, TA98, and TA100 and of *Escherichia coli* WP2 *uvrA* were exposed (plate incorporation method) to cyantraniliprole (DPX-HGW86-648, batch/lot number D100487-104, purity = 95.6%), in the presence and absence of S9 rat liver fraction, at 0 (DMSO), 50, 150, 500, 1500, and 5000 ug/plate and incubated for 48 to 72 hours at 37± 2°C. Positive controls were functional. There was no treatment-related increase in mutation frequency. Negative results indicate that under these test conditions the test article is not mutagenic in these test strains. **No adverse effects indicated. Acceptable.** (Corlett and Leung, 01/05/2012)

** 0410, 260646; "Cyantraniliprole (DPX-HGW86) Technical: *In Vitro* Mammalian Cell Gene Mutation Test (CHO/HGPRT Assay)" (Clarke, J.J., BioReliance, Rockville, MD, BioReliance Study Number AD10PN.782.BTL, 11/29/2010). 870.5300. Cultures of the Chinese hamster ovary (CHO-K1) cell line (HGPRT locus) were treated with Cyantraniliprole (DPX-HGW86) Technical (Batch/ Lot Number: D100487-104, purity = 95.6%), in the presence and absence of rat liver S-9 activation system, for 5 hours at concentrations of 0 (DMSO), 50, 100, 150, 250, and 500 ug/ml. Positive controls of ethyl methanesulphonate (EMS) (non-activated) and benzo(a)pyrene (B(a)P) (activated) were used and were functional. No evidence of mutagenic effects was observed in this mammalian forward mutation system. **No adverse effects indicated. Acceptable.** (Corlett and Leung, 01/11/2012)

** 0420, 260656; "Cyantraniliprole (DPX-HGW86) Technical: Bacterial Reverse Mutation Assay" (Wagner, V.O. and VanDyke, M.R., BioReliance, Rockville, MD for E.I. du Pont de Nemours and Company, DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE, BioReliance Study Number AC25SL.503.BTL, 06/11/2009). 870.5100. Triplicate cultures of *S. typhimurium* strains TA1535, TA1537, TA98, and TA100 and of *Escherichia coli* WP2 *uvrA* were exposed (plate incorporation method) to Cyantraniliprole (DPX-HGW86-425, batch/lot number 9182-1, purity = 97.0%), in the presence and absence of S9 rat liver fraction, at 0 (DMSO), 50, 150, 500, 1500, and 5000 ug/plate and incubated for 48 to 72 hours at 37± 2°C. Positive controls were functional. There was no treatment-related increase in mutation frequency. Negative results indicate that under these test conditions the test article is not mutagenic in these tested strains. **No adverse effects indicated. Acceptable.** (Corlett and Leung, 01/11/2012)

** 0424, 260660; "Cyantraniliprole (DPX-HGW86) Technical: CHO/HPRT Forward Mutation Assay with Duplicate Cultures" (Stankowski, L.F., Covance Laboratories Inc., Vienna, VA, Covance Study Number/Client Code: 8236883/1006174, 01/19/2011). 870.5300. Cultures of the Chinese hamster ovary (CHO-K1-BH4) cell line (HPRT locus) were treated with Cyantraniliprole (DPX-HGW86-412) Technical (Lot Number 9182-1, purity = 97.0%), in the presence and absence

of rat liver S-9 activation system, for 5 hours at concentrations (expression and selection phase of the study) of 0 (DMSO), 5.0, 50.0, 100, 500, 750, and 1000 ug/ml. Positive controls of ethyl methanesulphonate (EMS) (non-activated) and methylcholanthrene (MCA) (activated) were used and were functional. No evidence of mutagenic effects was observed in this mammalian forward mutation system. **No adverse effects indicated. Acceptable.** (Corlett and Leung, 01/20/2012)

CHROMOSOME EFFECTS

** 0354, 260577; "IN-JSE: *In Vitro* Mammalian Chromosome Aberration Test" (Gudi, R. and Rao, M., BioReliance, Rockville, MD for E.I. du Pont de Nemours and Company, DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE, BioReliance Study Number AC22CC.341.BTL, 03/12/2010). 870.5375. Duplicate cultures of human peripheral blood lymphocytes were treated with IN-JSE76 (a metabolite of cyantraniliprole, Lot (Dash) 005, purity = 93.8%), in the presence and absence of rat liver S9 activation system, for 4 hours at concentrations of 0 (DMSO), 625, 1250, and 2500 ug/ml and in the absence of rat liver S9 activation system for 20 hours at concentrations of 0, 313, 625, and 1000 ug/ml. Dividing lymphocytes were arrested at metaphase by treatment with Colcemid 18 hours after the initiation of treatment. Positive controls mitomycin C (MMC) (non-activated) and cyclophosphamide (CP) were used and were functional. No evidence of treatment-related chromosomal aberrations was observed in this test system. **No adverse effects indicated. Acceptable.** (Corlett and Leung, 12/01/2011)

** 0409, 260645; "Cyantraniliprole (DPX-HGW86) Technical: *In Vitro* Mammalian Chromosome Aberration Test" (Madraymootoo, W. and Jois, M., BioReliance, Rockville, MD, BioReliance Study Number AD10PN.341.BTL, 12/10/2010). 870.5375. Duplicate cultures of human peripheral blood lymphocytes were treated with Cyantraniliprole (DPX-HGW86-648), batch/lot number D100487-104, purity = 95.6%, in the presence of rat liver S9 activation system for 4 hours at concentrations of 0 (DMSO), 125, 250, and 600 ug/ml, and in the absence of rat liver S9 activation system for 4 hours at concentrations of 0, 125, 250, and 800 ug/ml and for 19 hours at concentrations of 31.3, 62.5, and 250 ug/ml. Dividing lymphocytes were arrested at metaphase by treatment with Colcemid 17 hours after the initiation of treatment. Positive controls mitomycin C (MMC) (non-activated) and cyclophosphamide (CP) were used and were functional. No evidence of treatment-related chromosomal aberrations was observed in this test system. **No adverse effects indicated. Acceptable.** (Corlett and Leung, 01/09/2012)

** 0421, 260657; "Cyantraniliprole (DPX-HGW86) Technical: *In Vitro* Mammalian Chromosome Aberration Test" (Gudi, R. and Rao, M., BioReliance, Rockville, MD for E.I. du Pont de Nemours and Company, DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE, BioReliance Study Number AC25MV.341.BTL, 07/07/2009). 870.5375. Duplicate cultures of human peripheral blood lymphocytes were treated with Cyantraniliprole (DPX-HGW86-425) Technical (Batch/Lot Number 9182-3B, purity = 97.7%) in the presence of rat liver S9 activation system for 4 hours at concentrations of 0 (DMSO), 250, 500, and 700 ug/ml, and in the absence of rat liver S9 activation system for 4 hours at concentrations of 0, 125, 250, and 800 ug/ml and for 20 hours at concentrations of 62.5, 125, and 500 ug/ml. Dividing lymphocytes were arrested at metaphase by treatment with Colcemid 18 hours after the initiation of treatment. Positive controls mitomycin C (MMC) (non-activated) and cyclophosphamide (CP) were used and were functional. No evidence of treatment-related chromosomal aberrations was observed in this test system. **No adverse effects indicated. Acceptable.** (Corlett and Leung, 01/13/2012)

** 0422, 260658; "Cyantraniliprole (DPX-HGW86) Technical: *In Vitro* Mammalian Chromosome Aberration Test" (Gudi, R. and Rao, M., BioReliance, Rockville, MD for E.I. du Pont de Nemours and Company, DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE, BioReliance Study Number AC25SL.341.BTL, 07/07/2009). 870.5375. Duplicate cultures of human peripheral blood lymphocytes were treated with Cyantraniliprole (DPX-HGW86-412) Technical (Batch/Lot Number 9182-1, purity = 97.0%) in the presence and in the absence of rat liver

S9 activation system for 4 hours at concentrations of 0 (DMSO), 250, 500, and 1000 ug/ml, and in the absence of rat liver S9 activation system for 20 hours at concentrations of 125, 250, and 500 ug/ml. Dividing lymphocytes were arrested at metaphase by treatment with Colcemid 18 hours after the initiation of treatment. Positive controls mitomycin C (MMC) (non-activated) and cyclophosphamide (CP) were used and were functional. No evidence of treatment-related chromosomal aberrations was observed in this test system. **No adverse effects indicated. Acceptable.** (Corlett and Leung, 01/17/2012)

DNA DAMAGE

** 0425, 260661; "Cyantraniliprole (DPX-HGW86) Technical: Mouse Bone Marrow Micronucleus Test" (Donner, E.M., E.I. du Pont de Nemours and Company, DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE, Laboratory Project ID: DuPont-31373, 01/26/2011). 870.5395. Cyantraniliprole (DPX-HGW86-412) Technical (Batch/Lot Number 9182-1, purity = 97.0%) was prepared in 0.1% Tween-80 in 0.5% aqueous methylcellulose prepared with deionized water and administered in a single dose to 10 Crl:CD1 (ICR) mice per sex per dose at dose levels of 0 (vehicle only), 500, 1000, and 2000 (14 per sex at this dose) mg/kg. Also, 5 animals per sex were dosed with 40 mg/kg of the positive control compound cyclophosphamide. 5 animals per sex per dose were sacrificed 24 hours after dosing and 5 animals per sex per dose were sacrificed 48 hours after dosing; all positive control animals were sacrificed after 24 hours. After sacrifice, the bone marrow cells from the femurs were examined: polychromatic erythrocytes were evaluated for the presence of micronuclei and the ratio of polychromatic erythrocytes to normochromatic erythrocytes was determined for each dose level. No treatment-related effects were observed. The positive control was functional. In conclusion, the results of this study indicate that under these test conditions, the test article does not induce micronuclei formation in the bone marrow cells of Crl:CD1 (ICR) mice. **No adverse effects indicated. Acceptable.** (Corlett and Leung, 01/25/2012)

NEUROTOXICITY

Rat Acute Neurotoxicity Study

53160-0335; 260558; "DPX-HGW86 Technical: Acute Oral Neurotoxicity Study in Rats"; (L.A. Malley; E.I. duPont de Nemours & Co., Haskell Laboratory for Health & Environmental Sciences, Newark, DE; Project ID No. DuPont-16996; 4/19/06); Twelve rats/sex/group were dosed orally by gavage with 0 (vehicle: aqueous 0.5% methylcellulose), 250, 1000 or 2000 mg/kg of DPX-HGW86 Technical (batch no. DPX-HGW86-141; purity: 93.4%). The study animals were examined in the functional observational battery (FOB) and motor activity assessments prior to dosing, 2 hours after dosing (day 1) and on study days 8 and 15. Six animals/sex/group of this cohort were randomly chosen for histological examination of the nervous system. There was no treatment-related effect noted in FOB or motor activity assessments. No treatment-related lesions were identified in the neurohistological examination. **No adverse effect indicated. Rat Acute Oral Neurotoxicity NOEL: (M/F) 2000 mg/kg** (based upon the lack of treatment-related neurological effects noted for both sexes in the 2000 mg/kg group). **Study acceptable.** (Moore, 10/26/11)

Rat Subchronic Neurotoxicity Study

53160-0345; 260568; "DPX-HGW86 Technical: Subchronic Oral Neurotoxicity Study in Rats"; (P. Mukerji; E.I. du Pont de Nemours & Co., DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE; Project ID No. DuPont-191186; 2/5/09); Twelve Crl:CD (SD) rats/sex/group received 0, 200, 2000, or 20000 ppm of DPX-HGW86 Technical (batch no. DPX-HGW86-230; purity: 94.5%) in the diet for 13 weeks ((M) 0, 11.4, 115.7, 1195 mg/kg/day, (F) 0, 14.0, 137.0, 1404 mg/kg/day). There was no treatment-related effect upon the mean body weights and food consumption. The FOB and Motor Activity assessments at 4, 8 and 13 weeks of treatment did not reveal any treatment-related effects. No treatment-related lesions were evident in the histopathological examination. **No adverse effect indicated. Reported Rat

Subchronic Neurotoxicity NOEL: (M/F) 20000 ppm ((M) 1195 mg/kg/day, (F) 1404 mg/kg/day) (based on the lack of treatment-related effects noted for both sexes in the 20000 ppm treatment group). Previously reviewed as study unacceptable and possibly upgradeable to acceptable if more recent positive control studies are submitted or if it is documented that the staff who performed the cited positive control studies also performed the neurotoxicity assessments in this study. (Moore, 11/1/11). Record 265212 contains the results of positive control studies with carbaryl, triadimefon, trimethyltin, and acrylamide in rats used to validate functional observational battery (FOB) and motor activity (MA) assessment procedures in the performing laboratory and certify and/or recertify the personnel involved. The in-life portions of these assays were performed from January 12 to February 3, 2009 (chronologically at the end or just after completion of record 260568). The procedures were validated. The study is upgraded to acceptable. (Green, 8/6/12).

RAT METABOLISM

53160-0334; 260557; ¹⁴C- DPX-HGW86: Absorption, Distribution, Metabolism and Excretion in Male and Female Rats"; (S.A. Gannon; E.I. duPont de Nemours & Co., DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE; Project ID No. DuPont-16995;1/15/09, revised 12/2/2010); Various cohorts of four Sprague-Dawley rats /sex/group were dosed orally by gavage with 10 or 150 mg/kg of either (Cyano-¹⁴C) DPX-HGW86 (lot no. 3503-242, specific activity: 16.95 uCi/mg, radiochemical purity: 99%) or (Pyrazole-¹⁴C) DPX-HGW86 (lot no. 3503-247, specific activity: 15.33 uCi/mg, radiochemical purity: 99%) and pharmacokinetic, mass balance, tissue distribution and bile duct cannulation studies were performed. Unlabeled DPX-HGW86 (lot no. 141, purity: 93.3%) was used to adjust the specific activity of the dosing preparations. In the pharmacokinetic study, the elimination half lives (T_{1/2}) for the males ranged from 42 to 62 hours, irrespective of the treatment level. For the females, at the 10 mg/kg treatment levels, the T_{1/2} values were 117 and 129 hours, diminishing to 65 and 80 hours at the 150 mg/kg treatment levels. The t_{max} values ranged between 1.0 and 2.5 hours for both test materials and treatment levels. The C_{max} values ranged from 5 to 10 times greater in the 150 mg/kg treatment groups in comparison to the 10 mg/kg treatment group values. The AUC (area under the curve) values were approximately 2 to 3 times greater for the females than the males in each of the treatment cohorts. In the material balance study, for the 10 mg/kg treatment groups, excretion in the urine constituted 21 to 35% of the administered dose as compared to 47 to 62% of the administered dose which was recovered in the feces. For the 150 mg/kg groups, the balance shifted further towards fecal excretion with 12 to 15% of the administered dose recovered in the urine and 78 to 80% in the feces. Excretion of the radiolabel was more rapid from the males with 65 to 74% of the administered dose recovered within the first 24 hours. For the females, the rapidity of excretion was affected by the treatment level. For the 10 mg/kg cohort, 50 to 55% of the administered dose was recovered within the first 24 hours. The percentage of recovery in this time interval was reduced to 30% for the 150 mg/kg treatment groups. In the bile duct cannulation study, 28 to 37% of the administered radiolabel was recovered in the bile of the 10 mg/kg males. The percentage of the dose recovered in the bile of the 150 mg/kg male cohort ranged from 12 to 16%. For the 10 mg/kg females, 16 to 27% was recovered in the bile, decreasing to 10 to 11% of the dose in the bile of the females in the 150 mg/kg treatment groups. Absorption of the administered dose ranged from 76 to 80% for the 10 mg/kg males and from 63 to 75% for the 10 mg/kg females. For the 150 mg/kg cohort, the absorption of the radiolabel was 39 to 40% for the males and 31 to 32% for the females. The tissue distribution studies demonstrated a time-course of diminished radiolabeling over the 7-day sampling period. The greatest percentage of the administered dose was sequestered in the G.I tract and contents and in the liver at the T_{max} and T_{max}/2 time points. Muscle and skin also demonstrated elevated levels at this two time points. The tissue/organs which had the greater concentrations of radiolabel included the liver and G.I. tract and contents, but also included the bladder, pituitary, thyroid and adrenal glands. Metabolism of the test material entailed hydroxylation of a methyl group at two sites on the molecule, ring closure and further conjugation

with glucuronide. Cleavage of the amide linkage in the molecule was also noted. **Study acceptable.** (Moore, 12/16/11)

53160-0336; 260559; ¹⁴C- DPX-HGW86: Disposition in Male and Female Rats during and after Multiple Dose Administration"; (S.A. Gannon; E.I. duPont de Nemours & Co., DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE; Project ID No. DuPont-17399; 7/16/09, revised, 12/2/10); Seven groups of three female Sprague-Dawley rats/group were dosed orally by gavage with 10 mg/kg/day of a 1:1 preparation of (Cyano-¹⁴C) DPX-HGW86 (lot no. 3503-242, specific activity: 16.95 uCi/mg, radiochemical purity: 99%) and (Pyrazole-¹⁴C) DPX-HGW86 (lot no. 3503-247, specific activity: 15.33 uCi/mg, radiochemical purity: 99%) for 4, 8, 11, or 14 days. Two groups of 3 males each were dosed for 14 days. For the groups which were dosed for 14 days, respective groups were euthanized on 1, 3, 7 or 12 days post-final dose. In the mass balance determination, 29 and 20% of the administered dose was recovered in the urine of the males and females, respectively. Sixty one and 62% of the administered dose was recovered in the feces of the males and females, respectively, by 7 days post-final dose. The half lives for the respective tissues/organs ranged from 2.6 (fat) to 5.7 (whole blood) days. The C_{max} values ranged from 4.7 ug equivalents/g in the muscle to 60.1 ug equivalents/g in the plasma. For all of the tissues/organs which were assayed, the tissue:plasma ratios were less than one by day 15 of the dosing regimen. The metabolic profile was quite similar to that observed in the single dose regimen. Metabolism entailed hydroxylation of a methyl group at two sites on the molecule, ring closure and further conjugation with glucuronide. Cleavage of the amide linkage in the molecule was also noted. **Study supplemental.** (Moore, 12/21/11)

SUBCHRONIC TOXICITY

Rat 2-Week Oral Toxicity Study

53160-0323; 260546; "Cyantraniliprole (DPX-HGW86) Technical: Repeated Dose Oral Toxicity 2-Week Gavage Study in Rats with Metabolism"; (D.L. Nabb; E.I. du Pont de Nemours & Co., DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE and Experimental Pathology Laboratories, Inc., Herndon, VA; Project ID No. DuPont-13430; 3/2/10); Five CrI:CD(SD) IGS rats/sex/group were dosed orally by gavage with 0 (vehicle: polyethylene glycol), 25, 300 or 1000 mg/kg/day of Cyantraniliprole (DPX-HGW86) Technical (lot no. DPX-HGW86-014; purity: 100%) for 14 days. This was the **main study cohort**. In addition, 18 males/group in the 25 and 300 mg/kg groups and 3 males in the 1000 mg/kg group were included in a **pharmacokinetic cohort**. In the **genotoxicity cohort**, a group of 5 males received a single dose of 2000 mg/kg of the test material and a positive control group of 5 males received a single dose of 20 mg/kg of cyclophosphamide. The treatments were administered on day 12 of the study. These animals were included with the animals in the main study cohort in the genotoxicity evaluation. No deaths resulted from the treatment. There were no treatment-related effects upon the mean body weight. There was no treatment-related effect upon the hematology, clinical chemistry or urinalysis parameters. The mean absolute and relative liver and adrenal weights of the females in the 1000 mg/kg group were greater than the control values (p<0.05). There was no treatment-related lesions noted in the histopathology. Cytochrome P450 isoform IAI was increased in the liver of the 25 mg/kg males and above. The P450 isoform 2B1 was increased in the liver of the 25 mg/kg females and above and in the liver of the 1000 mg/kg males. Peroxisomal beta-oxidation in the liver was not affected by the treatment. The treatment did not affect the serum thyroid hormone levels. In the genotoxicity evaluation, there was apparently no effect upon the presence of micronuclei in the reticulocytes (data were not presented in the report). The pharmacokinetic parameters were peculiar in that the C_{max} value for the 25 mg/kg group was greater than that observed for either the 300 or 1000 mg/kg groups and the AUC values for the three groups were comparable. No explanation was provided for that observation. The test material was recovered in the fat of the study animals in the 25 and 300 mg/kg groups up to 72

hours post-dose. **No adverse effect indicated. Rat 2-Week Oral Toxicity NOEL:** (M/F) < 25 mg/kg/day (based upon the increased levels of certain cytochrome P450 isoforms in the liver of both sexes). **Study supplemental.** (Non-guideline). (Moore, 10/12/11)

Rat 4-Week Dietary Toxicity Study

53160-0326; 260549; "DPX-HGW86 Technical: Repeated Dose Oral Toxicity, 28-Day Feeding Study in Rats"; (C. Carpenter; E.I. du Pont de Nemours & Co., DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE; Project ID No. DuPont-15206; 3/20/09); Five CrI:CD(SD) rats/sex/group received 0, 600, 2000, 6000 or 20000 ppm of DPX-HGW86 Technical (batch no. DPX-HGW86-085; purity: 92.7%) in the diet for 28 days ((M) 0, 52.8, 174.8, 527.8, 1776 mg/kg/day, (F) 0, 61.6, 188.1, 594.8, 1953 mg/kg/day). No deaths resulted from the treatment. The mean body weights and food consumption of the study animals were not affected by the treatment. In the hematology evaluation, the red blood cell count, hemoglobin concentration and hematocrit of the males in the 6000 and 20000 ppm groups were less than the control values (NS or $p < 0.05$). Ophthalmology and urinalysis did not reveal any treatment-related effects. In the clinical chemistry evaluation, the mean serum bilirubin levels for both sexes in all of the treatment groups were less than that of the control group animals (NS or $p < 0.05$). The cytochrome P450 content in the 6000 and 20000 ppm females was elevated in comparison to the control group females ($p < 0.05$). The activity of the liver enzyme, UDP-glucuronyl transferase, was increased for the 2000 ppm males and above ($p < 0.05$). The relative mean liver weights of both sexes in all of the treatment groups were greater than the control values (NS or $p < 0.05$). Likewise, the mean relative thyroid weights for both sexes in all of the treatment groups were greater the control values (NS or $p < 0.05$). In the histopathology evaluation, a dose-related increase in the incidence of centrilobular hypertrophy was evident for both sexes in all of the treatment groups ((M) 0: 0/5 vs. 600: 1/5, 2000: 3/5, 6000: 5/5, 20000: 5/5, (F) 0: 0/5 vs. 600: 1/5, 2000: 4/5, 6000: 3/5, 20000: 5/5)). Hypertrophy of the follicular cells was noted in both sexes of the 2000 ppm groups and above and in the 600 ppm male group ((M) 0: 0/5 vs. 600: 1/5, 2000: 3/5, 6000: 3/5, 20000: 4/5, (F) 0: 0/5 vs. 2000: 1/5, 6000: 1/5, 20000: 4/5). Target organs: liver and thyroid glands. **No adverse effect indicated. Rat 28-Day Dietary Toxicity NOEL:** (M/F) <600 ppm ((M) 52.8 mg/kg/day, (F) 61.6 mg/kg/day) (based upon treatment-related effects on the livers and/or thyroids of both sexes in the 600 ppm group); **Study supplemental.** (Moore, 10/17/11)

Rat Subchronic Dietary Toxicity Study

53160-0330,-0331; 260553, 260554; "DPX-HGW86 Technical: Subchronic Toxicity, 90-Day Feeding Study in Rats"; (C. Carpenter; S.A. Gannon; E.I. du Pont de Nemours & Co., Haskell Laboratory for Health & Environmental Sciences, Newark, DE; Project ID No. DuPont-16993; 7/23/07, amended, 4/6/11); Ten CrI:CD(SD) rats/sex/group received 0, 100, 400, 3000 or 20000 ppm of DPX-HGW86 Technical (batch no. DPX-HGW86-141; purity: 93.4%) in the diet for at least 92 days ((M) 0, 5.7, 22.4, 168.3, 1146.8 mg/kg/day, (F) 0, 6.9, 26.6, 202.1, 1345.5 mg/kg/day). A satellite cohort of 5 animals/sex/group were treated for 28 days. The concentrations of the parent compound and specific metabolites were analyzed in the plasma of these animals. No treatment-related deaths occurred during the study. The mean body weight gain of both sexes in the 3000 and 20000 ppm groups was less than the control group values (NS). There was no apparent treatment-related effect upon food consumption. The ophthalmological examination, hematological evaluation and urinalysis did not reveal any treatment-related effects. Serum bilirubin levels were lower for both sexes in all of the treatment groups after 6 and 13 weeks of treatment in comparison to the control group (NS or $p < 0.05$). Other clinical parameters were affected by the treatment in the 20000 ppm female treatment group (cholesterol (more), triglycerides (less), albumin (less), globulin (more) ($p < 0.05$)). The serum T4 and T3 levels were reduced both sexes in the 400 group and above at either 4 or 13 weeks ($p < 0.05$). The serum TSH level for the 20000 ppm males was greater than the control group value after 13 weeks of treatment

($p < 0.05$). The liver cytochrome P450 content of both sexes in the 3000 and 20000 ppm groups was elevated above those values for the control group after 13 weeks of treatment (NS, $p < 0.05$). The activity of the liver enzyme, UDP-glucuronyl transferase, was increased for both sexes in the 3000 ppm and 20000 ppm groups and for the females in the 400 ppm group after 13 weeks of treatment and ($p < 0.05$). The mean relative liver weights of both sexes in the 400 ppm group and above were greater than the control values by the termination of the study ($p < 0.05$). The mean absolute liver weights also demonstrated a dose-related increase for the most part as well. The mean absolute and relative thyroid weights of the 20000 ppm females were greater than the control values (NS, $p < 0.05$). The mean absolute and relative testes weights of the 20000 ppm males were greater than those of the control group (NS, $p < 0.05$). In the histopathological examination, hepatocellular hypertrophy of the liver was noted for both sexes in the 3000 and 20000 ppm groups and for the females in the 400 ppm group by the termination of the study. Hypertrophy of the follicular cells in the thyroid was noted for both sexes in the 20000 ppm group and for the females in the 400 and 3000 ppm groups. Microvesiculation was present in the adrenal gland of both sexes in the 3000 and 20000 ppm groups. In the satellite cohort, one metabolite, IN-MLA84, was the predominant compound recovered in the plasma in a dose-related manner at concentrations ranging from 16.3 to 259.5 ug/ml. The parent compound was the next most prominent moiety and ranged from 0.36 to 6.0 ug/ml across the treatment groups. **No adverse effect indicated. Rat Subchronic Dietary Toxicity NOEL: (M/F) 100 ppm ((M) 5.7 mg/kg/day, (F) 6.9 mg/kg/day)** (based upon reduced serum thyroid hormone levels of both sexes and increased hepatocellular hypertrophy of the females in the 400 ppm group). **Study acceptable.** (Moore, 10/24/11)

Rat 4-Week Repeated Dosing Dermal Toxicity Study

53160-0349; 260572; "Cyantraniliprole (DPX-HGW86) Technical: 28 Day Repeat Dermal Application Study in Rats"; (C. Lowe; Eurofins/Product Safety Laboratories, Dayton, NJ; Study No. 25531; 4/7/09, amended, 4/23/09); The skin of 10 Sprague-Dawley rats/sex/group was exposed to 0, 100, 300, or 1000 mg/kg/day of Cyantraniliprole (DPX-HGW86) Technical (batch no. DPX-HGW86-230; purity: 94.5%) for 6 hours/day at least for 29 days under an occlusive wrap. No deaths resulted from the treatment. There was no treatment related effect upon the mean body weights or food consumption throughout the treatment period. No treatment-related clinical signs or localized dermal irritation responses were evident throughout the treatment period. There were no treatment-related effects noted in the hematology or ophthalmology. The serum bilirubin levels were reduced for the females in all of the treatment groups ($p < 0.05$). The mean absolute and relative adrenal weights of the males were increased in the 1000 mg/kg group ($p < 0.05$ and 0.01, respectively). No treatment-related lesions were revealed in the histopathological evaluation. Although a statistically significant reduction in serum bilirubin levels of the females in all of the treatment groups and a statistically-significant increase in the absolute and relative adrenal weights of the 1000 mg/kg males was noted, there was no concomitant effect which indicated a possible injury to the livers or adrenals of these animals. **No adverse effect indicated. Rat 4-Week Repeated Dose Dermal Toxicity NOEL: (M/F) 1000 mg/kg/day** (based upon the lack of treatment-related effects in both sexes of the 1000 mg/kg treatment group); **Study acceptable.** (Moore, 11/14/11)

Rat 4-Week Immunotoxicity Study

** 53160-0350; 260573; "Cyantraniliprole (DPX-HGW86) Technical: 28-Day Immunotoxicity Feeding Study in Rats"; (D. Hoban; E.I. du Pont de Nemours & Co., DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE; Project ID No. DuPont-21467; 4/10/09); Ten CrI:CD (SD) rats/sex/group received 0, 20, 200, 2000 or 20000 ppm of Cyantraniliprole (DPX-HGW86) Technical; batch no. DPX-HGW86-230; purity: 94.5%) in the diet for 28 or 29 days ((M) 0, 1.7, 17, 166, and 1699 mg/kg/day, (F) 0, 1.8, 18, 172 and 1703 mg/kg/day). On study day 22 (males) or 23 (females), the tail vein of the study animals was

injected with 0.5 ml of 4×10^8 sheep red blood cells (SRBC)/ml. Primary humoral function was evaluated by analyzing for the SRBC-specific IgM levels in the serum by means of an enzyme-linked immunosorbent assay (ELISA). No deaths resulted from the treatment. There was no treatment-related effect upon the mean body weights or food consumption. No treatment-related clinical signs were evident. There was no treatment-related effect upon the mean absolute or relative brain, thymus or spleen weights. The treatment did not suppress the primary humoral response to SRBC. **No adverse effect indicated. Rat 28-Day Immunotoxicity NOEL:** 20000 ppm (M) 1699 mg/kg/day, (F) 1703 mg/kg/day (based upon the lack of treatment-related effects at the highest treatment level); **Study acceptable.** (Moore, 11/21/11)

Dog 4-Week Dietary Toxicity Study

53160-0327; 260550; "DPX-HGW86: 28-Day Oral Palatability Study in Dogs"; (E.M Lockett; MPI Research, Inc., Mattawan, MI; Study No. 125-052; 2/21/07); Two beagle dogs/sex/group received 0, 1000, 10000 or 40000 ppm DPX-HGW86 Technical (batch no. DPX-HGW86-085; purity: 92.7%) in the diet for 28 days ((M) 0, 34.8, 311.1, 1043 mg/kg/day, (F) 0, 35.1, 335.4, 1240 mg/kg/day) . One of the males in the 40000 ppm group was suffering from Canine Juvenile Polyarteritis Syndrome. Some of the clinical parameters which were assayed were affected by his condition. The mean body weight and food consumption of both sexes in all of the treatment groups was affected in a dose-related manner. There was no apparent treatment-related effect upon the hematology parameters. In the clinical chemistry evaluation, the terminal serum alkaline phosphatase activity was elevated in both sexes in all of the treatment groups. The terminal serum albumin concentrations was reduced in both sexes of all of the treatment groups. The terminal alanine aminotransferase activity in the serum of the 40000 ppm females was greater than the control value. Serum cholesterols levels were lower for the 10000 ppm males and the 10000 and 40000 ppm females. The total cytochrome P450 and isoform 2B1/2 contents were greater in the livers of both sexes of all of the treatment groups. The terminal serum T3 levels of both sexes in all of the treatment groups were less than those of the control group. The mean absolute and relative liver weights of both sexes in the 10000 and 40000 ppm groups and the females in the 1000 ppm were greater than the control group values. The mean absolute and relative testicular weights of all of the treatment group males were greater than the control group values. The histopathological evaluation of the tissues/organs did not reveal any apparent treatment-related lesions. For the 40000 ppm males, the data were not particularly useful because of the poor health of one of the animals. **No adverse effect indicated. Dog 4-Week Dietary Toxicity NOEL:** (MF) < 1000 ppm ((M) < 34.8 mg/kg/day, (F) < 35.1 mg/day/day) (based upon the multiple treatment-related effects noted for both sexes in the 1000 ppm treatment group). **Study supplemental.** (Moore, 10/19/11)

Dog Subchronic Dietary Toxicity Study

53160-0332, -0333; 260555, 260556; "DPX-HGW86 Technical: 90-Day Dietary Toxicity Study in Dogs"; (E.M. Lockett; MPI Research, Inc., Mattawan, MI; Study No. 125-055; 7/27/07); Four beagle dogs/sex/group received 0, 30, 100, 1000 or 10000 ppm of DPX-HGW86 Technical (batch no. DPX-HGW86-141; purity: 93.4%) in the diet for at least 92 days ((M) 0, 0.98, 3.08, 31.9, 280.9 mg/kg/day, (F) 0, 0.97, 3.48, 34.3, 293.8 mg/kg/day). One male in the 10000 ppm group was found dead on day 52. The cause of death was attributed to Canine Juvenile Polyarteritis Syndrome (CJPS). Other dogs were also possibly suffering from CJPS. The mean body weight gain of both sexes in the 10000 ppm group was less than that of the control group over the course of the study (NS, $p < 0.01$). The mean food consumption of these animals was less than that of the control group as well. There were no apparent treatment-related clinical signs. In the hematology evaluation, by the end of the treatment period the red blood cell count, hemoglobin concentration and hematocrit of both sexes in the 10000 ppm group were less than the respective

control values (NS). In the clinical chemistry evaluation, the mean serum calcium levels for both sexes in the 10000 ppm group and the males in the 1000 ppm group were less than the control values by week 12 of the study ($p < 0.01$). The serum alkaline phosphatase activity levels were elevated for both sexes in the 100 ppm group and above in a dose-related manner (NS, $p < 0.05$ or 0.01). The serum albumin concentrations of both sexes in the 1000 and 10000 ppm groups were less than those of the control group throughout the study ($p < 0.05$ or 0.01). The total serum protein levels were affected in a similar manner. The serum cholesterol levels of both sexes in the 10000 ppm group were lower than the control group values by the conclusion of the study (NS, $p < 0.05$ or 0.01). The mean relative liver weights were increased in a dose-related manner for both sexes in all of the treatment groups (NS, $p < 0.05$ or 0.01). The mean absolute liver weights were similarly higher except that of the 10000 ppm males which was less than the mean liver weight of the 1000 ppm males. The 10000 ppm animals experienced much less body weight gain over the course of the study and thereby less of an increase in liver weight. The mean absolute and relative kidney weights of both sexes in the 10000 ppm group were greater than the control group values (NS, $p < 0.05$). In the histopathology, hyperplasia of the bile duct was noted in the liver of both sexes in the 10000 ppm group ((M) 0: 0/4 vs. 10000: 3/3, (F) 0: 0/4 vs. 10000: 3/4). Necrosis of individual hepatocytes or focal necrosis was noted in one of three males and 3 of 4 females in the 10000 ppm group. Moderate or severe atrophy of the thymus was present in one of the four males (lesion was present in male dying on day 52) and one of the 4 females in the 10000 ppm group. Analysis of the plasma for the presence of the parent compound and various metabolites revealed that the predominant moiety which was recovered was the unmetabolized parent compound. The concentrations increased in a dose-related manner and ranged from 1.74 to 51.9 ug/ml at treatment levels between 30 and 10000 ppm. **Possible adverse effect:** hepatic necrosis; **Dog Subchronic Dietary Toxicity NOEL:** (M/F) 30 ppm ((M) 0.98 mg/kg/day, (F) 0.97 mg/kg/day) (based upon increased levels of serum alkaline phosphatase activity and increased relative liver weights noted for both sexes in the 100 ppm group); **Study acceptable.** (Moore, 10/26/11)

Mouse 4-Week Dietary Toxicity

53160-0325; 260548; "DPX-HGW86 Technical: Repeated Dose Oral Toxicity, 28-Day Feeding Study in Mice"; (C. Carpenter; E.I. du Pont de Nemours & Co., DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE; Project ID No. DuPont-15205; 3/20/09); Five Crl:CD-1(ICR)BR mice/sex/group received 0, 300, 1000, 3000 or 7000 ppm of DPX-HGW86 Technical (batch no. DPX-HGW86-085; purity: 92.7%) in the diet for 4 weeks ((M) 0, 52.8, 175.2, 528.1, 1261 mg/kg/day, (F) 0, 63.4, 212.4, 663.5, 1476 mg/kg/day). Another five animals/sex/group received the test material in the diet for the same time period. Peroxisomal β -oxidation activity and microsomal P450 protein levels were assayed in the livers of these animals. No deaths occurred during the study. There was no treatment-related effect upon the mean body weights or food consumption. No treatment-related effects were noted in the hematology evaluation or on plasma protein levels. The mean absolute and relative liver weights of both sexes in the 3000 and 7000 ppm groups were greater than the control values ($p < 0.05$). Minimal focal necrosis was noted in the livers of the 7000 ppm group (both males and females) (0: 1/10 vs. 7000: 4/10). Peroxisomal β -oxidation in the liver was not apparently affected by the treatment. The microsomal P-450 levels were elevated in the livers of both sexes in the 3000 and 7000 ppm groups ($p < 0.05$). **Possible adverse effect:** focal necrosis in the liver; **Mouse 4-Week Dietary Toxicity NOEL:** (M/F) 1000 ppm ((M) 175.2 mg/kg/day, (F) 212.4 mg/kg/day) (based upon the elevation of cytochrome P450 content in the livers of both sexes in the 3000 ppm group); **Study supplemental.** (Moore, 10/14/11)

Mouse 4-Week Immunotoxicity Study

** 53160-0351; 260574; "Cyantraniliprole (DPX-HGW86) Technical: 28-Day Immunotoxicity Feeding Study in Mice"; (D. Hoban; E.I. du Pont de Nemours & Co., DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE; Project ID No. DuPont-21468; 4/11/11); Ten Crl:CD1(ICR) mice/sex/group received 0, 20, 150, 1000 or 7000 ppm of Cyantraniliprole (DPX-HGW86) Technical; batch no. DPX-HGW86-230; purity: 94.5%) in the diet for 28 or 29 days ((M) 0, 3.0, 23, 154, and 1065 mg/kg/day, (F) 0, 4.1, 32, 224 and 1386 mg/kg/day). On study day 22 (males) or 23 (females), the tail vein of the study animals was injected with 0.2 ml of 4×10^8 sheep red blood cells (SRBC)/ml. Primary humoral function was evaluated by analyzing for the SRBC-specific IgM levels in the serum by means of an enzyme-linked immunosorbent assay (ELISA). No deaths resulted from the treatment. There was no treatment-related effect upon the mean body weights or food consumption. No treatment-related clinical signs were evident. There was no apparent treatment-related effect upon the mean absolute or relative brain, thymus or spleen weights. The treatment did not suppress the primary humoral response to SRBC. **No adverse effect indicated. Mouse 28-Day Immunotoxicity NOEL:** 7000 ppm ((M) 1065 mg/kg/day, (F) 1386 mg/kg/day) (based upon the lack of treatment-related effects at the highest treatment level); **Study acceptable.** (Moore, 11/21/11)

Mouse Subchronic Dietary Toxicity Study

53160-0328, -0329; 260551, 260552; "DPX-HGW86 Technical: Subchronic Toxicity, 90-Day Feeding Study in Mice"; (S.A. MacKenzie, S.A. Gannon; E.I. du Pont de Nemours & Co., Haskell Laboratory for Health & Environmental Sciences, Newark, DE and Experimental Pathology Laboratories, Inc., Sterling, VA; Project ID No. DuPont-16992; 4/17/07, amended, 4/6/11); Ten Crl:CD1(ICR) mice/sex/group received 0, 50, 300, 1000 or 7000 ppm of DPX-HGW86 Technical (batch no. DPX-HGW86-141; purity: 93.4%) in the diet for at least 97 days ((M) 0, 7.2, 47.1, 149.8, 1092 mg/kg/day, (F) 0, 9.7, 58.1, 204.0, 1344 mg/kg/day). A satellite cohort of 5 animals/sex/group received the same treatment levels in the diet for 63 days. The concentrations of the parent compound and specific metabolites were analyzed in the plasma of these animals. One male in the 1000 ppm group was found dead on day 62; one female in the 300 ppm was found dead on day 72. Deaths were not apparently treatment-related. There was no treatment-related effect upon body weight gain or food consumption. The ophthalmological examination did not reveal any treatment-related lesions. There were no treatment-related effects in the hematological evaluation or the plasma protein levels. The mean absolute and relative liver weights of the 7000 ppm males and the mean relative liver weights of the 1000 and 7000 ppm females were greater than the respective control values ($p < 0.05$). In the histological examination, hepatocellular, centrilobular hypertrophy was noted for 2 males and 9 females in the 7000 ppm group and for 1 female in the 1000 ppm group. Necrosis, focal, was also noted for four females and 1 male in the 7000 ppm group and one male and one female in the 1000 ppm group and one female in the 300 ppm group. Microvesiculation was observed in the adrenal glands of all of the male treatment groups (50: 3/10, 300: 5/10, 1000: 4/10, 7000: 7/10). In the satellite cohort, one metabolite, IN-MLA84, was the predominant compound recovered in the plasma at concentrations ranging from 111 to 500 ug/ml for all of the treatment groups. The parent compound was the next most prominent moiety and ranged from 0.09 to 9.0 ug/ml across the treatment groups. **Possible adverse effect:** liver necrosis. **Mouse Subchronic Dietary Toxicity NOEL:** (M) < 50 ppm (<7.2 mg/kg/day) (based upon microvesiculation in the adrenal glands of the 50 ppm males) (F) 50 ppm (9.7 mg/kg/day) (based upon the incidence of necrosis in the liver of the 300 ppm females); **Study acceptable.** (Moore, 10/20/11).

MECHANISTIC STUDIES

53160-0352; 260575; "Cyantraniliprole (DPX-HGW86) Technical: Adrenal and Thyroid Mechanistic: 90-Day Feeding Study in Rats"; (S.A Mackenzie; E.I. du Pont de Nemours & Co., DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE, Experimental Pathology Laboratories, Inc. Durham, NC and Laboratory for Advanced Electron and Light Optical Methods, College of Veterinary Medicine, North Carolina State University, Raleigh, NC; Project ID No. DuPont-24319; 5/20/10); Fifteen female Sprague-Dawley rats/group received either 0 or 20000 ppm of Cyantraniliprole (DPX-HGW86) Technical (batch no. DPX-HGW86-230; purity: 94.5%) in the diet for 29 days (0, 1903 mg/kg/day). Fifteen male Sprague-Dawley rats/group received 0 (identified as Group 1), 0 (identified as Group 3) or 20000 ppm of the test material in the diet for 93 days (0, 0, 1230 mg/kg/day). Liver and thyroid biochemical parameters were assayed for the females at the end of the 29-day treatment period. For the males, Group 1 control and the 20000 ppm males received an iv injection of 12.5 ug/animal of ACTH (adrenocorticotrophic hormone) on day 93. Control Group 3 received an injection of isotonic saline. One hour later, blood was drawn from the orbital sinus and all of the animals were euthanized. No deaths resulted from the treatment. The mean body weight gain of both sexes in the 20000 ppm group was less than that of the control groups (NS, $p < 0.05$). The mean food consumption was not affected by the treatment. For the females, among the thyroid assessment parameters, the mean serum TSH level of the 20000 ppm group was greater than that of the control group ($p < 0.05$). The mean serum T4 level of this group was less than the control value ($p < 0.05$). In the liver, the 5'-iodinase activity level of the 20000 ppm group females was less than that of the control group ($p < 0.05$). The UDP-glucuronyltransferase activity in the liver of these females was elevated in relationship to the control females ($p < 0.05$). The absolute and relative liver weights of the 20000 ppm females were greater than the control group values ($p < 0.05$). In the histopathological assessment, minimal hypertrophy of the thyroid gland was noted for 5 of the 15 animals in the 20000 ppm group. For the males, the adrenal response after ACTH treatment was comparable for both the control and treated animals with an increase in serum corticosterone levels in both groups. Minimal microvesiculation of the zona fasciculata of the adrenal gland was noted for 4 of the 10 males in the 20000 ppm group. **No adverse effect indicated. Rat 4-Week Dietary NOEL:** (F) < 20000 ppm (1903 mg/kg/day) (based upon the treatment-related effects on the thyroid and liver of the 20000 ppm females); **Rat Subchronic Dietary NOEL:** (M) < 20000 ppm (1230 mg/kg/day) (based upon the microvesiculation noted in the adrenal gland of the 20000 ppm males); **Study supplemental** (non-guideline study). (Moore, 11/28/11)

53160-0357; 260580; "Cyantraniliprole (DPX-HGW86) Technical: *In Vitro* Thyroid Peroxidase Inhibition"; (S.I. Snajdr; E.I. du Pont de Nemours & Co., DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE; Project ID No. DuPont-27123; 9/9/10); The potential of cyantraniliprole to inhibit thyroid peroxidase was evaluated *in vitro* with a microswine thyroid preparation. Concentrations of Cyantraniliprole (DPX-HGW86) Technical (lot no. DPX-HGW86-230; purity: 94.5%) ranging from 2 to 400 uM in 10% DMSO were incubated with homogenized thyroid tissue from the Yucatan pig (microswine) under specified conditions. A positive control, propylthiouracil (PTU), was employed in the study as well. Cyantraniliprole gave no evidence of inhibiting thyroid peroxidase over the range of treatment levels. An IC50 value of 7.3 uM was determined for PTU. **Study supplemental.** (Moore, 12/8/11)

53160-0362; 260585; "Cyantraniliprole (DPX-HGW86) Technical: Adrenal Mechanistic Study, 90-Day Feeding Study in Mice"; (S.A. MacKenzie; E.I. du Pont de Nemours & Co., DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE, Experimental Pathology Laboratories, Inc., Durham, NC, Laboratory for Advanced Electron and Light Optical Methods, College of Veterinary Medicine, North Carolina State University, Raleigh, NC; Project ID No. DuPont-29405; 6/24/10); Ten male Crl:CD-1 mice/group received 0 or 7000 ppm of

Cyantranilprole (DPX-HGW86) Technical (batch no. DPX-HGW86-141; purity: 91.5%) in the diet for 93 days (0, 1120 mg/kg/day). No deaths occurred during the treatment period. The mean body weight gain was less than that of the control group (NS). Food consumption was not affected by the treatment. There was no apparent treatment-related effect upon the corticosterone or creatinine levels and the corticosterone/creatinine ratio in the urine. The mean absolute and relative adrenal weights were not affected by the treatment. Light and electron microscopic examination of the adrenal tissue did not reveal any treatment-related lesions. These observations were in contrast to those of the previous mouse subchronic dietary study (vol. no. 53160-0328, rec. no. 260551) in which microvesiculation in the adrenal gland was noted for the treated mice. **Study supplemental** (non-guideline study). (Moore, 12/9/11)

STUDIES ON METABOLITES

Rat Acute Oral Toxicity Studies

53160-0324; 260547; "IN-N5M09: Acute Oral Toxicity Study in Mice - Up and Down Procedure"; (C. Carpenter; E.I. du Pont de Nemours & Co., DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE; Project ID No. DuPont-30713; 9/13/10); Three female CD1 mice were dosed orally by gavage with 5000 mg/kg of IN-N5M09 (lot no. IN-N5M09-003; purity: 99.9%). No deaths occurred. No treatment-related clinical signs were noted. No treatment-related lesions were evident in the necropsy examination. LD50 (F) > 5000 mg/kg; Toxicity Category IV. **Study acceptable.** (Moore, 10/3/11)

53160-0356; 260579; "IN-JSE76: Acute Oral Toxicity Study - Up and Down Procedure in Rats"; (S.D. Oley; Eurofins/ Product Safety Laboratories, Dayton, NJ; Study No. 26453; 2/12/09); One female Sprague-Dawley rat each was dosed orally by gavage with 175, 550 or 1750 mg/kg of IN-JSE76 (lot no. IN-JSE76-005; purity: 93.8%). An additional group of 3 females was treated with 5000 mg/kg of the test material. No deaths resulted from the treatment. No treatment-related clinical signs were evident. In the necropsy examination, no treatment-related lesions were noted. LD50 (F) > 5000 mg/kg; Toxicity Category IV; **Study acceptable.** (Moore, 9/27/11)

53160-0400; 260636; "IN-PLT97: Acute Oral Toxicity Study in Mice - Up-and-Down Procedure"; (C. Carpenter; E.I. du Pont de Nemours & Co., DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE; Project ID No. DuPont-30571; 9/1/10); Three female CrI:CD1(CR) mice were dosed orally by gavage with 5000 mg/kg of IN-PLT97 (metabolite of Cyantranilprole) (lot no. E115107-77B; purity: 98.1%). No deaths occurred. No treatment-related clinical signs were noted. No treatment-related lesions were evident in the necropsy examination. LD50 (F) > 5000 mg/kg; Toxicity Category IV. **Study acceptable.** (Moore, 10/10/11)

Rat 4-Week Dietary Toxicity Study

53160-0360, -0426; 260583, 260662; "IN-JSE76: Repeated-Dose Oral Toxicity Study, 28-Day Feeding Study in Rats"; (S. S. Anand; E.I. du Pont de Nemours & Co., DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE; Project ID No. DuPont-28842; 5/28/10, amended 4/6/11). Ten CrI:CD(SD) rats/sex/group received 0, 100, 400, 3000 or 20000 ppm of IN-JSE76 (metabolite of Cyantranilprole) (lot no. IN-JSE76-006; purity: 97.8%) in the diet for 4 weeks ((M) 0, 7.05, 28.8, 211.5, 1445 mg/kg/day, (F) 0, 7.67, 31.0, 231.9, 1471 mg/kg/day). No deaths resulted from the treatment. There were no treatment-related effects upon body weight gain or food consumption. The ophthalmological examination, hematological evaluation and urinalysis did not reveal any treatment-related effects. Although the concentration of the total bile acids in the serum of both sexes in the 20000 ppm group was less than the control group values

($p < 0.05$), the toxicological significance of this observation was not readily apparent. No other related parameter were affected. There was no treatment-related effect upon the absolute or relative organ weights. The histopathological examination did not reveal any treatment-related effects. There was no apparent treatment-related effect upon the thyroid hormone parameters or the hepatic biochemical parameters. The parent compound and one metabolite (IN-K5A78) were recovered in the plasma of the 3000 and/or 20000 ppm treatment groups. There was no apparent sex-related difference in plasma concentrations of these compounds. **No adverse effect indicated. Rat 28-Day Dietary Toxicity NOEL:** (M/F) 20000 ppm ((M) 1445 mg/kg/day, (F) 1471 mg/kg/day) (based upon the lack of treatment-related effects noted in both sexes of the 20000 ppm group). **Study supplemental.** (Moore, 12/8/11)

Gene Mutation Studies

0359, 260582; "IN-N5M09: Bacterial Reverse Mutation Assay" (Wagner, V.O. and VanDyke, M.R., BioReliance, Rockville, MD, BioReliance Study Number AC29WT.503.BTL, 09/24/2009). 870.5100. Triplicate cultures of *S. typhimurium* strains TA1535, TA1537, TA98, and TA100 and of *Escherichia coli* WP2 *uvrA* were exposed (plate incorporation method) to IN-N5M09-003 (an analogue of cyantraniliprole) (Batch/ Lot Number: D100855-058, purity = 99.9%), in the presence and absence of S9 rat liver fraction, at 0 (propylene glycol), 50, 150, 500, 1500, and 5000 ug/plate and incubated for 48 to 72 hours at $37 \pm 2^\circ\text{C}$. Positive controls were functional. There was no treatment-related increase in mutation frequency. Negative results indicate that under these test conditions the test article is not mutagenic in these tested species. **No adverse effects indicated. Acceptable.** (Corlett and Leung, 12/21/2011)

0355, 260578; "IN-JSE: Bacterial Reverse Mutation Assay" (Wagner, V.O. and VanDyke, M.R., BioReliance, Rockville, MD for E.I. du Pont de Nemours and Company, DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE, BioReliance Study Number AC22CC.503.BTL, 02/25/2009). 870.5100. Triplicate cultures of *S. typhimurium* strains TA1535, TA1537, TA98, and TA100 and of *Escherichia coli* WP2 *uvrA* were exposed (plate incorporation method) to IN-JSE76 (a metabolite of cyantraniliprole, Lot (Dash) 005, purity = 93.8%), in the presence and absence of S9 rat liver fraction, at 0 (DMSO), 50, 150, 500, 1500, and 5000 ug/plate and incubated for 48 to 72 hours at $37 \pm 2^\circ\text{C}$. Positive controls were functional. There was no treatment-related increase in mutation frequency. Negative results indicate that under these test conditions the test article is not mutagenic in these tested species. **No adverse effects indicated. Acceptable.** (Corlett and Leung, 12/06/2011)

0401, 260637; "IN-PLT97: Bacterial Reverse Mutation Assay" (Wagner, V.O. and Jois, M., BioReliance, Rockville, MD, BioReliance Study Number AD08NK.503.BTL, 10/20/2010). 870.5100. Triplicate cultures of *S. typhimurium* strains TA1535, TA1537, TA98, and TA100 and of *Escherichia coli* WP2 *uvrA* were exposed (plate incorporation method) to IN-PLT97-003 (an analogue of cyantraniliprole) (Batch/ Lot Number: E115107-77B, purity = 98.1%), in the presence and absence of S9 rat liver fraction, at 0 (DMSO), 50, 150, 500, 1500, and 5000 ug/plate and incubated for 48 to 72 hours at $37 \pm 2^\circ\text{C}$. Positive controls were functional. There was no treatment-related increase in mutation frequency. Negative results indicate that under these test conditions the test article is not mutagenic in these tested strains. **No adverse effects indicated. Acceptable.** (Corlett and Leung, 12/22/2011)

0402, 260638; "IN-PLT97: *In Vitro* Mammalian Chromosome Aberration Test" (Madraymootoo, W. and Jois, M., BioReliance, Rockville, MD, BioReliance Study Number AD08NK.341.BTL, 04/12/2011). 870.5375. Duplicate cultures of human peripheral blood lymphocytes were treated with IN-PLT97-003 (an analogue of cyantraniliprole), Batch/ Lot Number: E115107-77B, purity = 98.1%, in the presence of rat liver S9 activation system for 4 hours at concentrations of 0 (DMSO), 50, 100, and 500 ug/ml and in the absence of rat liver S9 activation system for 4 and 20 hours at

concentrations of 0, 100, 400, and 1550 ug/ml. Dividing lymphocytes were arrested at metaphase by treatment with Colcemid 18 hours after the initiation of treatment. Positive controls mitomycin C (MMC) (non-activated) and cyclophosphamide (CP) were used and were functional. No evidence of treatment-related chromosomal aberrations was observed in this test system. **No adverse effects indicated. Acceptable.** (Corlett and Leung, 12/30/2011)

0403, 260639; "IN-PLT97: *In Vitro* Mammalian Cell Gene Mutation Test (CHO/HGPRT Assay)" (Clarke, J.J., BioReliance, Rockville, MD, BioReliance Study Number AD08NK.782.BTL, 11/19/2010). 870.5300. Cultures of the Chinese hamster ovary (CHO-K1) cell line (HGPRT locus) were treated with IN-PLT97 (an analogue of cyantraniliprole, Batch/ Lot Number: E115107-77B, purity = 98.1%), in the presence and absence of rat liver S-9 activation system, for 5 hours at concentrations of 0 (DMSO), 10, 25, 50, 100, and 150 ug/ml. Positive controls of ethyl methanesulphonate (EMS) (non-activated) and benzo(a)pyrene (B(a)P) (activated) were used and were functional. No evidence of mutagenic effects was observed in this mammalian forward mutation system. **No adverse effects indicated. Acceptable.** (Corlett and Leung, 01/04/2012)