

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
Pyrifluquinazon

Chemical Code # 6073 Tolerance # 53161

9 March 2012

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, possible 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, possible adverse effect |
| Gene mutation: | No data gap, no adverse effect |
| Chromosome effects: | No data gap, possible adverse effect |
| DNA damage: | No data gap, no adverse effect |
| Neurotoxicity: | Not required at this time |

Toxicology one-liners are attached.

All record numbers through 261005 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T120309 prepared by H. Green

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

CHRONIC TOXICITY, RAT

****53161-0067 260988**, “NNI-0101 Technical: Repeated Dose 1-Year Oral Toxicity Study in Rats”, (M. Kuwahara, The Institute of Environmental Toxicology, Ibaraki, Japan, Study No. IET 03-0061, 25 September 2006). Twenty Fischer (F344/DuCrj) rats per sex per group received NNI-0101 technical (pyrifluquinazon technical) (98.0%) in the diet at 0 (basal diet), 100, 350, and 1300 ppm for 52 weeks. Group mean average NNI-0101 intake during the treatment period was 4.08, 14.4, and 56.6 mg/kg/day for males and 4.97, 18.0, and 65.6 mg/kg/day for females at 100, 350, and 1300 ppm, respectively. In females, detailed clinical observation results showed a significant increase in rearing in the open field at week 25 at 100 ppm, at week 47 at 350 ppm, and at weeks 3, 8, 9, 10, 16, 19, 22, and 28 at the high dose level vs controls. Additionally, forelimb and hindlimb grip strength were significantly decreased for high dose females vs controls. Group mean bodyweights were significantly reduced for females at 350 and 1300 ppm at weeks 44 and 52 compared to controls. Group mean urinalysis results included significant decreases in ketones at weeks 13 and 26; significant increases in urine volume (week 26 and 51) and in protein (week 51) for high dose males and significant increases in urine pH and specific gravity at weeks 13 and 51 in high dose females vs controls. Group mean significant hematology changes included decreases in hemoglobin concentration, mean corpuscular volume, and mean corpuscular hemoglobin at weeks 13, 26, and 52 (hematocrit was also decreased at weeks 26 and 52) in high dose males (increases in reticulocyte count and bone marrow nucleated cell count (bone marrow nucleated cell count was due to an increase of erythroblastic cells), considered an adaptive response to anemia, were also noted) vs controls. Additionally, significant decreases in group mean corpuscular volume and mean corpuscular hemoglobin were noted for high dose females and mid dose males at weeks 13, 26, and 52 vs controls and for low and mid dose males and females at weeks 26 and 52. Also, a significant shortening of group mean prothrombin time was noted in mid and high dose females at week 52 vs controls. Group mean serum chemistry changes included significant increases in gamma glutamyl transpeptidase activity (weeks 13, 26, and 52) and significant decreases in blood urea nitrogen and triglyceride (weeks 13 and 26), calcium and chloride (weeks 13, 26, and 52) for high dose females vs controls (glucose and total cholesterol were also significantly increased for 350 ppm females at weeks 13, 26, and 52 (significant increases were noted for total cholesterol at the low dose level too)). In high dose males, significant decreases in group mean total cholesterol (weeks 26 and 52), triglyceride (weeks 13, 26, and 52), total bilirubin, direct bilirubin (week 52), sodium (week 26), and chloride (weeks 26 and 52) were noted vs controls. Significant increases in group mean relative liver weights were noted for both sexes at 100, 350, and 1300 ppm; in group mean relative kidney weights in both sexes at 350 and 1300 ppm; in group mean relative heart weight in high dose males and mid and high dose females; and in group mean relative thyroid and spleen weights in high dose females vs controls. NOEL = 100 ppm (4.08 mg/kg/day in males and 4/97 mg/kg/day in females) based on kidney weights. No adverse effect. Acceptable. (Green and Leung, 12/13/11).

CHRONIC TOXICITY, DOG

****53161-0063, 0064 260981, 260982**, “NNI-0101 Technical: Repeated Dose 1-Year Oral Toxicity Study in Dogs”, (M. Kuwahara, The Institute of Environmental Toxicology, Ibaraki, Japan, Study No. IET-03-0068, November 21, 2006). Four Beagle dogs per sex per group received NNI-0101 technical (pyrifluquinazon technical) (98.0%) orally (gelatin capsules) at 0 (empty gelatin capsule), 1.5, 5, and 15 mg/kg/day for 52 weeks. All animals survived to scheduled necropsy. No treatment-related effects were recorded for clinical signs, bodyweight, bodyweight gain, food consumption, ophthalmology, urinalysis, and macroscopy at any treatment level.

Group mean blood biochemistry results at the high dose level included significantly increased alkaline phosphatase activity in males (treatment weeks 13 and 26) and females (weeks 13, 26, and 52); significantly reduced albumin in males (week 52); and significantly increased glucose in females (week 13) vs controls. At 5 mg/kg/day, significant reductions in group mean albumin and total cholesterol were noted for males at week 52 vs controls. Significant increases in group mean relative thyroid and liver weights were noted for high dose males and in group mean relative spleen weights for mid dose males vs controls. Treatment-related histopathology was indicated in the nasal cavity and liver of both sexes. In the nasal cavity, an increased incidence of mononuclear cell infiltration (epithelial degeneration/necrosis was noted at the severe grade) was noted in 1/4, 2/4, and 3/4 males and in 3/4, 2/4, and 4/4 females at 1.5, 5, and 15 mg/kg/day, respectively, vs the control incidence (0/4 for both sexes) (the high dose incidence for females was significantly different from the control and a severity grade of severe was noted in 1 mid dose male and 1 high dose female (slight to moderate severity grades were noted for all other animals) (record 260982 contains a discussion/characterization of the lesions). In liver, the incidence of centrilobular hepatocellular hypertrophy was significantly increased at 15 mg/kg/day for males (4/4) and females (4/4) vs controls (0/4). At 5 mg/kg/day, 2 males had severe retinal atrophy and nerve fiber degeneration in the optic nerve in both eyes (animals were not littermates). NOEL males and females < 1.5 mg/kg/day (nasal cavity histopathology). **Possible adverse effect:** mononuclear cell infiltration, epithelial degeneration/necrosis in the nasal cavity. Acceptable. (Green and Leung, 11/22/11).

53161-0065, 066 260985, 260986, "NNI-0101 Technical: Repeated Dose 1-Year Oral Toxicity Study and 6-Month Recovery Study in Dogs", (K. Shibuya, Nisseiken Co., Ltd., Tokyo, Japan, Study No. D-27, 12 December 2008). Four Beagle dogs per sex per group received NNI-0101 technical (pyrifluquinazon technical) (98.0%) orally (gelatin capsules) at 0 (empty gelatin capsule), 0.15, 0.5, and 5 mg/kg/day for 52 weeks. An additional group of 4 females received NNI-0101 technical at 5 mg/kg/day for 52 weeks followed by a 26 week non treatment recovery period. All animals survived to scheduled termination. No treatment-related changes were indicated for clinical signs, urinalysis, ophthalmology, hematology, and gross pathology. Group mean bodyweight gain was significantly decreased in high dose males for treatment weeks 1 to 26 and 1 to 39 compared to controls. Histopathology results included mononuclear cell infiltration in the olfactory portion of the nasal cavity in 2 males (mild grade) and in 1 female (moderate grade) at 5 mg/kg/day (ns compared to controls). The lesion was characterized as infiltration and aggregation of mononuclear cells, mainly lymphoid cells, in the olfactory mucosa in the absence of abnormal changes in any olfactory glands or nerve fiber bundles. Recovery phase females were free of nasal cavity lesions. Record number 260986 is an additional immunological phase of this study performed on blood and tissue samples using cell-mediated and antibody-mediated immunological evaluations. Flow cytometric analysis of blood lymphocyte subsets (pan-T cell, pan-B cell, helper-T cell, cytotoxic T cell) and measurement of serum immunoglobulin (IgE, IgM, IgG) were carried out for blood samples collected pretreatment and at treatment weeks 13, 26, 39, and 52 and flow cytometric analysis of lymphocyte subsets (pan-B cell, pan-T cell, IgE positive B cell, helper T cell, and cytotoxic T cell) of the submandibular lymph node (proximal lymph node to the nasal cavity) was determined at necropsy (week 52) for all groups. No immunological effect was indicated. Supplemental data. (Green and Leung, 12/1/11).

ONCOGENICITY, RAT

****53161-0069 260991**, "NNI-0101 Technical: Carcinogenicity Study in Rats", (M. Kuwahara, The Institute of Environmental Toxicology, Ibaraki, Japan, Study No. IET 03-0062, 28 September 2006). Fifty Fischer (F344/DuCrj) rats per sex per group received NNI-0101 technical (pyrifluquinazon technical) (98.0%) in the diet at 0 (basal diet), 100, 350, and 1300 ppm for 104 weeks. Group average NNI-0101 intake during the treatment period was 3.53, 12.5, and 48.5 mg/kg/day for males and 4.51, 16.4, and 60.2 mg/kg/day for females at 100, 350, and 1300 ppm,

respectively. Clinical observations at 1300 ppm included significant increases in the incidence of opacity of the eye in males (34/50 vs 4/50) and females (47/50 vs 5/50) and in mass in the tail of males (10/50 vs 3/50) vs controls. Group mean bodyweight was significantly reduced at 1300 ppm for males (from week 64 to the end of treatment) and females (from week 36 to the end of treatment) and at 350 ppm for males (from week 68 to the end of treatment) and females (from week 32 to the end of treatment) vs controls (and for low dose males sporadically (weeks 20, 28 to 32, 68 to 84, and at week 104)). At the high dose level, group mean food consumption was significantly increased for males (from week 3 to 60, and week 68) and females (weeks 3 to 9, 12, 16, and 24) and significantly decreased for males (weeks 76, 84, 92, and 104) and females (weeks 48 and 52 and from week 68 to 100) vs controls. At 1300 ppm, necropsy revealed a significant increase in opacity of the eye in both sexes (scheduled + unscheduled deaths and terminal sacrifice animals). Also, in mid and high dose males, significant increases in the incidence of softening of the epididymis (terminal sacrifice and scheduled + unscheduled deaths) and masses in the testes (terminal sacrifice + unscheduled deaths and unscheduled deaths) were noted. Group mean relative brain, heart, liver, kidney, thyroid (females only) and adrenal weights (males only) were significantly increased for both sexes at 1300 ppm vs controls (group mean relative liver weights were also increased for mid dose males). Group mean relative epididymis weights were significantly reduced for mid and high dose males vs controls. Neoplastic results included a significant increase in Leydig cell tumors in the testis of mid and high dose males (scheduled + unscheduled deaths). Significant decreases were noted in the incidence of C-cell adenoma of the thyroid in both sexes (scheduled + unscheduled deaths and terminal sacrifice animals), adenoma of the posterior lobe of the pituitary in females (scheduled + unscheduled deaths and terminal sacrifice animals), and mononuclear cell leukemia in males (unscheduled deaths) at 1300 ppm vs controls (mononuclear cell leukemia was also significantly reduced for mid and high dose females (scheduled + unscheduled deaths)). The incidence of Leydig tumors in the testis of males was 82%, 76%, 98%, and 94% at 0, 100, 350, and 1300 ppm, respectively (the historical control incidence range at the performing laboratory (IET) was 68% to 86%). Non-neoplastic lesions at the high dose level included significant increases in the incidence of atrophy of the mammary gland (females only, scheduled + unscheduled deaths, and terminal sacrifice animals), atrophy of striated muscle fiber (males only, scheduled and unscheduled deaths), rhinitis in the nasal cavity of males (scheduled + unscheduled deaths, and terminal sacrifice animals), centrilobular hepatocellular hypertrophy in liver of both sexes (all fates), diffuse hepatocellular fatty change in liver of females (all fates), bile duct hyperplasia in liver of females (terminal sacrifice, scheduled + unscheduled deaths), acinar cell vacuolation, focal acinar cell atrophy, and foci of cellular alteration in pancreas of females (all fates), chronic nephropathy (both sexes, all fates) and tubular basophilic change (females only, terminal sacrifice) in kidneys, atrophy of epididymis, seminal vesicles, coagulating glands, and prostate in males (all fates), atrophy of the ovary in females (all fates), and retinal atrophy and cataract in both sexes (all fates) compared to controls. Chronic NOEL = 100 ppm (3.53 mg/kg/day for males and 4.51 mg/kg/day for females) based on bodyweight. Carcinogenicity NOEL = 100 ppm (Leydig cell tumors in testis of males). **Possible adverse effect:** an increased incidence of Leydig cell tumors in the testis of males. Acceptable. (Green and Leung, 1/11/12).

ONCOGENICITY, MOUSE

****53161-0068 260990**, "NNI-0101 Technical: Carcinogenicity Study in Mice", (M. Kuwahara, The Institute of Environmental Toxicology, Ibaraki, Japan, Study No. IET 03-0064, 27 September 2006). Fifty-two ICR (Crj:CD-1) mice per sex per group received NNI-0101 (pyrifluquinazon technical) (98.0%) in the diet at 0 (basal diet), 60, 250, and 1000 ppm for 18 months. Group average NNI-0101 intake during the treatment period was 6.25, 27.1, and 122 mg/kg/day for males and 5.82, 25.0, and 120 mg/kg/day for females at 60, 250, and 1000 ppm, respectively. Cumulative mortality during the 78 week treatment period was 17/51, 19/52, 20/52, and 20/52 for males and 10/52, 14/52, 14/52, and 9/52 for females at 0, 60, 250, and 1000 ppm,

respectively. A significant increase in the incidence of loss of fur was noted for mid and high dose males and high dose females (tactile hair loss was also significantly increased for mid and high dose males). Group mean bodyweights were significantly reduced at 1000 ppm for males (at week 2 and from week 4 to the end of treatment) and females (from week 4 to the end of treatment) and at 250 ppm for males (from week 8 to 56) vs controls. At 1000 ppm, necropsy revealed significant increases in the incidence of loss of tactile hair, hair loss on the skin, livers dark in color, livers with spots, livers with coarse surface, pelvic dilatation of kidney, and spots and masses on the testes in males; and hair loss in females vs controls (mid dose males also had significantly increased hair loss on the skin). At 1000 ppm, significant increases were noted in group mean relative liver and heart weights for both sexes and in relative brain, kidney and thyroid weights in females vs controls. Neoplastic lesions included a significantly increased incidence of interstitial cell tumor in testis of high dose males (in both unscheduled deaths (5/20) and terminal sacrifice animals (7/32)) vs controls (0/51). Non-neoplastic lesions noted at 1000 ppm included significant increases in intracytoplasmic eosinophilic bodies in respiratory epithelial cells (both sexes) and in olfactory epithelial cells (males) in the nasal cavity; glandular epithelial cell hyperplasia in the mammary gland (females); centrilobular hepatocyte hypertrophy and single cell hepatocyte necrosis (both sexes) and focal hepatocyte necrosis (males) in liver; diffuse acinar cell atrophy in the pancreas (females); interstitial cell hyperplasia in the testis (males); endometrium hyperplasia in the uterine horn (females; and also significantly increased in mid dose females at terminal sacrifice); follicular cell hypertrophy in the thyroid (both sexes); and subcapsular cell hyperplasia in the adrenals (males; it was also significantly increased in mid dose males) vs controls. Chronic NOEL = 60 ppm (6.25 mg/kg/day for males and 5.82 mg/kg/day for females) based on bodyweight and uterine histology. Carcinogenicity NOEL = 250 ppm (27.1 mg/kg/day in males and 25.0 mg/kg/day in females) interstitial cell tumors in testis. **Possible adverse effect:** an increased incidence in interstitial cell tumors in testis of males. Acceptable. (Green and Leung, 12/22/11).

REPRODUCTION, RAT

**53161-0061, 0062 260979, 260980, "NNI-0101 Technical: Reproductive Toxicity Study in Rats", (H. Hojo, The Institute of Environmental Toxicology, Ibaraki, Japan, Study No. IET 03-0070, 21 September 2006). Twenty-four F0 and F1 Sprague-Dawley (Jcl:SD) rats per sex per group received NNI-0101 technical (pyrifluquinazon technical) (98.0%) in the diet at 0 (untreated diet), 30, 150, and 750 ppm through 2 generations with 1 litter per generation. Overall group mean NNI-0101 intake during the study for F0 parents was 1.79, 8.94, and 45.5 mg/kg/day for males and 2.72, 13.8, and 67.2 mg/kg/day for females and, the values for F1 parents were 1.94, 9.66, and 48.8 mg/kg/day for males and 2.77, 14.1, and 69.0 mg/kg/day for females at 30, 150, and 750 ppm, respectively. Group mean bodyweight was significantly reduced for high dose F0 females at treatment weeks 2 to 10, gestation days 0 to 20, and lactation days 7 and 14 and, for high dose F1 females at weeks 5 to 10 and gestation days 0 and 20 vs controls. Group mean bodyweight gains were also significantly reduced for F0 females during treatment weeks 0 to 10 and gestation days 0 to 20 and for F1 females during treatment weeks 0 to 10 at 750 ppm vs controls. Group mean food consumption was significantly decreased in F0 females at 750 ppm for treatment weeks 6 and 9 and for lactation days 0 to 7, 7 to 14, and 14 to 21 and, in F1 high dose females, for treatment weeks 6 and 7 and for lactation days 7 to 14 and 14 to 21 vs controls. The F1 group mean days of age and bodyweight at preputial separation were significantly increased for males (bodyweight was also significantly increased at 150 ppm) and the bodyweight at vaginal opening significantly decreased for females at 750 ppm vs controls. The group mean estrous cycle length was significantly increased for F1 females at 150 and 750 ppm. Group mean duration of gestation (days) was significantly increased for F0 females at 750 ppm vs controls (22.7 vs 22.0 days). The % of sperm with normal morphology was significantly reduced for F0 and F1 parental males at 750 ppm vs controls. Necropsy revealed significantly increased incidences of dark in color liver in F0 females (9/24 vs 0/24) and pelvic dilatation in

kidneys of F1 females (6/24 vs 0/24) at 750 ppm vs controls. Significant increases in group mean relative liver, kidney, testes, and thyroid weights were recorded at 750 ppm for F0 males and in adrenal gland and testes of high dose F1 males vs controls. At the high dose level, F0 females had significantly increased group mean relative pituitary, liver, kidney, and thyroid weights and F1 female group mean relative liver, adrenal gland, kidney, uterus, and thyroid weights were significantly increased (relative brain weights were significantly decreased) vs controls. F1 female group mean relative kidney and thyroid weights were also significantly increased at 150 ppm vs controls. Histology revealed significant increases in centrilobular hepatocyte hypertrophy in liver of F0 males (7/24 vs 0/24) and females (12/24 vs 0/24) at 750 ppm vs controls (thyroid follicular cell hypertrophy was also significantly increased in F0 females at the high dose vs controls). Histopathology of F1 females included significant increases in thyroid follicular cell hypertrophy (21/24 vs 0/24), centrilobular hepatocyte hypertrophy in liver (11/24 vs 0/24), and dilatation of the renal pelvis (7/24 vs 0/24) at 750 ppm vs controls. The mean number of F1a (10.7 vs 15.0) and F2a pups (8.6 vs 13.1) delivered was significantly reduced at 750 ppm vs controls. Group mean pup weights were significantly reduced for F1a males and females for lactation days 7, 14, and 21 and for F2a males and females on lactation day 21 at 750 ppm vs controls and for F2a females on lactation days 7, 14, and 21 at 150 ppm vs controls. The group mean absolute and relative (ratio of the anogenital distance to a cubic root of the bodyweight) anogenital distances (AGD) were significantly decreased for F1a and F2a male pups at 750 ppm vs controls. At 750 ppm, necropsy of pups revealed significant increases in litter incidences of hypospadias in F1a males and in dilatation of the renal pelvis in F2a pups vs controls. Parental NOEL = 30 ppm (1.79 to 1.94 mg/kg/day for males and 2.72 to 2.77 mg/kg/day for females). (increased kidney and thyroid weights). Pup NOEL = 30 ppm (reduced pup weights). Record 260979 is a dose range-finding study. Reproductive NOEL = 150 ppm (8.94 to 9.66 mg/kg/day for males and 13.8 to 14.1 mg/kg/day for females) (reduced number of pups per litter). No adverse reproductive effect. Acceptable. (Green and Leung, 11/18/11).

53161-0061 260979, "NNI-0101 Technical: Reproductive Toxicity Study in Rats, A Dose Range-Finding Study", (H. Hojo, The Institute of Environmental Toxicology, Ibaraki, Japan, Study No. IET 03-0069, 31 August 2005). Eight Jcl:SD rats per sex per group received NNI-0101 technical in the diet at 0 (basal diet), 100, 500, 1250, and 2500 ppm from 3 weeks prior to mating through weaning of F1a offspring. Subsequently, seven or eight F1 parental rats per sex per group were treated at 0, 100, and 500 ppm through lactation day 4 of F2a offspring. Overall group mean F0 and F1 achieved dosages during the study were 5.90 (F0 males), 7.36 (F1 males), 10.86 (F0 females), and 7.70 (F1 females) mg/kg/day at 100 ppm, respectively; 30.0 (F0 males), 36.7 (F1 males), 52.6 (F0 females), and 39.1 (F1 females) mg/kg/day at 500 mg/kg/day, respectively; and for F0 animals 75.7 mg/kg/day (males) and 97.8 mg/kg/day (females) at 1250 ppm, and 140.3 mg/kg/day (males) and 128.3 mg/kg/day (females) at 2500 ppm, respectively. The incidence of soiled fur in the nasorostral region was significantly increased in F0 females at 2500 ppm during the pre-mating period vs controls (5 vs 0 incidence). F0 group mean bodyweight was significantly decreased for males (for weeks 1 through 4) and females (during the 11 week treatment period) at 1250 ppm and, for both sexes at 2500 ppm, during the treatment period vs controls. F0 group mean food consumption was significantly reduced during the treatment period for males and females at 2500 ppm and for females at 1250 ppm vs controls. The F0 mating index at 2500 ppm (4/8, 50%) was significantly reduced compared to controls (8/8, 100%). At 2500 ppm, 4 copulations were noted but no pregnancies occurred in F0 females. Four of 8 F0 females at 1250 ppm delivered litters and the duration of gestation was significantly increased compared to controls. The number of implantation sites in F1 females was reduced at 100 and 500 ppm (statistically significant at 500 ppm) vs controls. Group mean live litter sizes on gestation day 0 were 14.1, 15.4, 14.7, 5.0 (statistically significant vs control), and 0 for F1a litters at 0, 100, 500, 1250, and 2500 ppm, respectively, and 14.2, 11.7, and 10.7 for F2a litters at 0, 100, and 500 ppm, respectively. The mean days of age at completion of preputial separation was significantly increased for F1a male pups at 500 ppm compared to controls (the age at completion of vaginal opening in females was comparable to controls). At

2500 ppm, significant increases in group mean relative brain, liver, kidney, uterus, and thyroid weights were noted for F0 males and females, and for pituitary, adrenal gland, testes, and seminal vesicles for F0 males vs controls. Significant increases were also noted for group mean relative liver weights in F0 males and females at 1250 ppm and for relative kidney, uterus, and thyroid weights in F0 females. Additionally, group mean relative liver, kidney, and thyroid weights were significantly increased in F0 females 500 ppm (and relative thyroid weights were significantly increased at 100 ppm). F0 and F1 parental necropsy results were unremarkable. F0 histopathology revealed centrilobular hypertrophy of hepatocytes in liver of all males and females at 1250 ppm and in one female at 500 ppm (2500 ppm animals were not evaluated). The mean number of F1a pups delivered was significantly reduced at 1250 ppm vs controls and nipple retention was significantly increased in male pups during lactation days 8 to 14. At 500 ppm, the sex ratio of F1a male pups to total pups was significantly reduced vs controls (0.388 vs 0.584). F1a male group mean pup weights were significantly reduced at 1250 ppm vs controls on lactation days 14 and 21. F1a pup necropsy results showed a significance increase in the litter incidence of dilatation of the renal pelvis at 1250 ppm vs controls. Unselected F1a group mean relative liver weights were significantly increased for male and female pups at 500 ppm vs controls and for male pups at 1250 ppm. F1a group mean relative thymus weights were significantly decreased for male and female pups at 1250 ppm vs controls. Histopathology of F1a unselected weanlings revealed hypertrophy of centrilobular hepatocytes in liver of male and female pups at 1250 ppm. Absolute and relative anogenital distances (AGD) in F2a male pups on lactation day 4 were significantly reduced at 500 ppm vs controls. Reproductive NOEL = 100 ppm (5.90 to 7.36 mg/kg/day for males and 7.70 to 10.86 mg/kg/day for females) (reduced pup sex ratio, reduced male pup day 4 AGD, reduced litter size). Supplemental data. (Green, 11/10/11) No worksheet.

TERATOLOGY, RAT

**53161-0058, 0060 260975, 260977, "NNI-0101 Technical: Teratogenicity Study in Rats", (H. Hojo, The Institute of Environmental Toxicology, Ibaraki, Japan, Study No. IET 03-0072, 9 March 2006). Twenty-four mated Jcl:SD female rats per group received NNI-0101 technical (pyrifluquinazon technical) (98.0%) by oral gavage at 0 (1% aqueous sodium carboxymethylcellulose), 5, 10, and 50 mg/kg/day on gestation days 6 through 19. All dams survived to scheduled necropsy. Group mean maternal bodyweight (on gestation days 9 to 20) and bodyweight gain (throughout the treatment period) were significantly reduced at 50 mg/kg/day compared to controls. Significant reductions in group mean maternal food consumption for gestation days 6 to 9 and 9 to 12 were noted at the high dose level vs controls. Maternal necropsy results were unremarkable. Twenty-three, 24, 23, and 24 females at 0, 5, 10, and 50 mg/kg/day produced live litters, respectively (live litter sizes were 15.3, 15.1, 14.7, and 13.9, respectively). Group mean fetal weights were significantly reduced for both sexes at 50 mg/kg/day vs controls and absolute and relative (adjusted for bodyweight) anogenital distances were significantly decreased for male fetuses at 10 and 50 mg/kg/day (absolute anogenital distance values for females were also significantly reduced at 50 mg/kg/day). At 10 and 50 mg/kg/day, the incidence of fetuses with skeletal variations (supernumerary ribs) was significantly increased compared to controls (the incidence was outside the historical control range). No treatment-related visceral changes were indicated. Record 260977 is a dose range-finding study. Maternal NOEL = 10 mg/kg/day (based on decreases in bodyweight and food consumption). Developmental NOEL = 5 mg/kg/day (based on reduced anogenital distance and increased skeletal variation). Teratogenicity was not indicated. Acceptable. (Green and Leung, 11/4/11).

53161-0060 260977, "NNI-0101 Technical: Teratogenicity Study in Rats, A Dose Range-Finding Study", (H. Hojo, The Institute of Environmental Toxicology, Ibaraki, Japan, Study No. IET 03-0071, 1 October 2004). Seven mated female Jcl:SD rats per group received NNI-0101

technical (pyrifluquinazon technical) (96.4%) by oral gavage at 0 (1% aqueous sodium carboxymethylcellulose), 5, 10, 50, and 100 mg/kg/day on gestation days 6 through 19. During the treatment period at 100 mg/kg/day: one dam was found dead on gestation day 12 and significant increases were noted for soiled fur (5 females) and eye discharge (4 females) vs controls (0 females); and 3 dams were noted with loss of locomotor activity from gestation day 10 vs controls (0 incidence). One high dose dam died during the post treatment period (gestation day 20). Significant decreases in group mean bodyweight (gestation days 12 through 20) and bodyweight gain (gestation days 6 through 20) were recorded at the high dose level vs controls. Bodyweight gains were also significantly reduced at 50 mg/kg/day for gestation days 6 to 9 and 6 to 18 vs controls. Group mean food consumption was significantly decreased at 100 mg/kg/day for gestation days 9 to 12, 12 to 15, 15 to 18, and 18 to 20 vs controls. Four dams were noted with total litter resorptions at 100 mg/kg/day. Fetal bodyweights were significantly reduced at 50 mg/kg/day compared to controls. Teratogenicity was not indicated. Maternal and fetal NOEL = 10 mg/kg/day (maternal bodyweight gains and fetal weights). Supplemental data. (Green, 11/2/11). (No worksheet).

TERATOLOGY, RABBIT

****53161-0057, 0059 260974, 260976**, "NNI-0101 Technical: Teratogenicity Study in Rabbits", (N. Shimizu, The Institute of Environmental Toxicology, Ibaraki, Japan, Study No. IET 03-0077, 7 June 2005). Twenty-five artificially inseminated female Japanese White rabbits (Kbl:JW) received NNI-0101 technical (pyrifluquinazon technical) (98.0%) by oral gavage at 0 (1% aqueous sodium carboxymethylcellulose), 5, 10, and 20 mg/kg/day on gestation days 6 to 27. All females survived to scheduled cesarean sectioning. No treatment-related maternal effects were noted for clinical signs and group mean bodyweight and food consumption compared to controls. Group mean maternal bodyweight gains were slightly reduced at 10 mg/kg/day (-21%) and 20 mg/kg/day (-36%) vs controls (ns) during gestation days 6 to 28. Twenty-three, 24, 21, and 19 live litters with mean live litter sizes of 8.3, 7.9, 8.3, and 6.5 resulted at 0, 5, 10, and 20 mg/kg/day, respectively (mean live litter size at 20 mg/kg/day was significantly reduced vs controls). Group mean fetal skeletal malformations were significantly increased at 20 mg/kg/day vs controls and included 1 fetus with a bent clavicle, another with a supernumerary lumbar arch, 2 fetuses with fused sternebra, and 2 with misaligned caudal vertebra (6 fetuses and 5 litters were effected). Record 260974 is a dose range-finding study. Maternal NOEL = 20 mg/kg/day. Developmental NOEL = 10 mg/kg/day (increased fetal skeletal malformations). **Fetal skeletal malformations were significantly increased and mean live litter size was significantly decreased at 20 mg/kg/day vs controls.** Acceptable. (Green and Leung, 11/8/11).

53161-0057 260974, NNI-0101 Technical: Teratogenicity Study in Rabbits, a Dose Range-Finding Study", (N. Shimizu, The Institute of Environmental Toxicology, Ibaraki, Japan, Study No. IET 03-0076, 22 April 2005). Eight artificially inseminated female Japanese White rabbits (Kbl:JW) received NNI-0101 technical (pyrifluquinazon technical) (98.0%) by oral gavage at 0 (1% aqueous sodium carboxymethylcellulose), 5, 20, 50, and 100 mg/kg/day on gestation days 6 to 27. At 100 mg/kg/day, significant reductions in group mean bodyweight (from gestation day 15 and thereafter), bodyweight gains and food consumption (gestation days 6 to 21) were noted compared to controls and six females were found dead during gestation days 15 to 23 and two females aborted on day 17. At 50 mg/kg/day, group mean bodyweight gains (gestation days 6 to 28) and food consumption (during gestation days 18 to 21) were significantly reduced vs controls and 3/8 females aborted during gestation days 18 to 24. At 20 mg/kg/day, group mean maternal bodyweight gains were significantly decreased for gestation days 6 to 28 vs controls. The number of live litters at Cesarean sectioning was 7, 7, 8, 5, and 0 and the mean live litter size was 6.3, 6.6, 6.0, 7.6, 0.0 at 0, 5, 20, 50, and 100 mg/kg/day, respectively. Group mean fetal weights were 36.3 g (males) and 38.1 g (females) at 0 mg/kg/day; 39.3 g (males) and 38.6 g (females) at 5 mg/kg/day; 39.1 g (males) and 39.5 g (females) at 20 mg/kg/day; and 35.1 g (males) and 36.0 g (females) at 50 mg/kg/day. Teratogenicity was not indicated. Twenty

mg/kg/day was chosen as the high dose level for the main study. Supplemental data. (Green, 11/7/11). No worksheet.

GENE MUTATION

****53161-0070 260992**, "Bacterial Reverse Mutation Test of NNI-0101", (K. Inagaki, Nihon Nohyaku Co., Ltd., Osaka, Japan, Report No. LSRC-T04-309A, 20 April 2005). Triplicate cultures of *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 *uvrA* were exposed to NNI-0101 (pyrifluquinazon technical) (98.0%), in the presence and absence of rat liver S9 mix, at 0 (DMSO), 15, 46.3, 139, 417, and 1250 µg/plate for 48 hours (at 37°C) using preincubation (cultures were treated and preincubated for 20 minutes prior to plating). Precipitation was noted at 417 and 1250 µg/plate and cytotoxicity was recorded at 417 µg/plate (slight background lawn diminution in *S. typhimurium* strain TA1537) and 1250 µg/plate (slight to clear background lawn diminution in all strains). There were no increases in the number of revertants per plate compared to solvent controls. Positive controls were functional. No adverse effect. Acceptable. (Green and Leung, 1/30/12)

CHROMOSOME EFFECTS

****53161-0071 260993**, "NNI-0101: *In vitro* Chromosome Aberration test in Cultured Chinese Hamster Cells", (K. Inagaki, Nihon Nohyaku Co., Ltd., Osaka, Japan, Report No. LSRC-T06-142A, 7 September 2006). Duplicate cultures of Chinese hamster lung fibroblasts (CHL/IU) were exposed to NNI-0101 technical (pyrifluquinazon technical) (98.0%) in the presence of S9 mix at 0 (DMSO), 100, 105, 110, 115, 120, and 125 µg/ml for 6 hours; and, in the absence of activation, at 0, 20, 35, 50, 65, and 80 µg/ml for 6 hours; at 0, 9.8, 14.8, 22.2, 33.3, and 50 µg/ml for 22 hours; and at 0, 17.5, 22.8, 29.6, 38.5, and 50 µg/ml for 44 hours. Cells treated for 6, 22, and 44 hours were harvested 22, 22, and 44 hours after the start of treatment, respectively. Two hours prior to harvest, colcemid solution (0.1 µg/ml) was added to each culture to arrest dividing cells in metaphase. The cell survival rate at the highest evaluated concentration in each treatment regime was 50% or less of the solvent control value (i.e., 31.5 % at 110 µg/ml and 44.3% at 115 µg/ml, +S9 mix, and 43.5% at 80 µg/ml and 41.6% at 65 µg/ml, -S9 mix, after the 6 hour treatment period; 43.9% at 22.2 µg/ml, -S9 mix, after the 22 hour treatment period; and 25.4% at 29.6 µg/ml, -S9 mix, after the 44 hour exposure period). There was no increase in structural chromosome aberrations after the 6 hour (-/+ S9 mix), 22 hour (-S9 mix), or 44 hour (-S9 mix) exposure periods. **Possible adverse effect:** the percentage of polyploidy cells was significantly increased after the 6 hour exposure period in the presence and absence of activation. Positive controls were functional. Acceptable. (Green and Leung, 1/31/12).

DNA DAMAGE

****53161-0072 260994**, "NNI-0101, Mouse Micronucleus Test, Amended Final Report", (C.E. Mason, Huntingdon Life Sciences Ltd., Huntingdon, Cambridgeshire, England, Report No. NHH 107/013537, 15 November 2001, amended 3 June 2003 (to remove a typographical error)). Ten [SPF] Sprague-Dawley CD-1 outbred albino mice received a single oral gavage dose of NNI-0101 technical (pyrifluquinazon technical) (99.0%) at 0 (1% w/v carboxymethylcellulose), 125, 250, and 500 mg/kg followed by bone marrow sampling of 5 per sex per group at 24 and 48 hours post-dosing. All animals survived to scheduled sampling time. At 500 mg/kg, clinical signs included: fast, deep, slow, and irregular respiration; unresponsiveness; flat and hunched posture; overactivity and underactivity; abnormal gait; partially closed eyes; piloerection; and prostate posture in both sexes (irregular respiration, flat posture, underactivity, abnormal gait, partially closed eyes, and piloerection were also observed in 250 mg/kg males). There was no increase in micronucleated polychromatic (immature) erythrocytes (PCEs). The mean percentage of PCEs to normochromatic erythrocytes was significantly decreased for males at 250 and 500 mg/kg at the

48 hour sampling time compared to the vehicle controls. No increase in cytogenetic damage was indicated. Positive controls were functional. Acceptable. (Green and Leung, 2/2/12).

SUBCHRONIC STUDIES

Dog 90-Day Oral (Gelatin Capsule) Toxicity Study

53161-0052, 0064 260967, 260982, "NNI-0101 Technical: Repeated Dose 90-Day Oral Toxicity Study in Dogs", (Y. Takeuchi, The Institute of Environmental Toxicology, Ibaraki, Japan, Study No. IET-03-0067, 12 September 2005). Four Beagle dogs per sex per group received NNI-0101 technical (pyrifluquinazon technical) (98.0%) orally (gelatin capsules) at 0 (empty gelatin capsule), 2, 5, and 30 mg/kg/day for 13 weeks. All animals survived to the end of the treatment period. No treatment-related changes were noted for clinical signs, detailed clinical observations, food consumption, ophthalmology, urinalysis, hematology, or necropsy results. A decreasing trend in group mean bodyweight gain was noted for males during the treatment period (group mean values were 1.5, 1.2, 0.9, and 0.8 kg at 0, 2, 5, and 30 mg/kg/day, respectively). Values for females were 1.1, 0.9, 0.5, and 0.8 kg, respectively vs controls (ns). Statistically significant serum chemistry changes included increases in group mean alkaline phosphatase (weeks 7 and 13) and glutamic pyruvic transaminase activities (week 13) and decreases in albumin and albumin/globulin ratio in both sexes (weeks 7 and 13 in males and week 13 in females) at 30 mg/kg/day. Additionally, at 5 mg/kg/day, group mean alkaline phosphatase activity was significantly increased in males at weeks 7 and 13. Group mean absolute and relative liver weights were significantly increased for both sexes at the high dose level vs controls. Histopathology results included significant increases in diffuse hepatocellular hypertrophy in livers of both sexes at 30 mg/kg/day vs controls. NOEL not determined at this time. Unacceptable and possibly upgradeable with submission of retrospective nasal cavity histology for this study cited in record 260982. (Green, 10/24/11).

Rat 90-Day Oral (Feeding) Toxicity Study

**53161-0051 260966, "NNI-0101 Technical: Repeated Dose 90-Day Oral Toxicity Study in Rats", (N. Nakshima, The Institute of Environmental Toxicology, Ibaraki, Japan, Study No. IET 03-0068, 16 March 2004). Ten Fischer (F344/DuCrj) rats per sex per group received NNI-0101 technical (pyrifluquinazon technical) (96.3%) in the diet at 0 (basal diet), 50, 100, 500, and 2500 ppm for 90 days. Overall average NNI-0101 technical intake during the treatment period was 2.89, 5.74, 29.3, and 155 mg/kg/day for males and 3.21, 6.44, 33.0, and 159 mg/kg/day for females at 50, 100, 500, and 2500 ppm, respectively. All animals survived to the end of the treatment period. At 2500 ppm, the incidence of bilateral red adhesive substance in the periocular region was significantly increased for both sexes (9/10 males and 8/10 females) at week 1 compared to controls (1/10 each sex). Treatment-related functional observations included significant increases in motor activity during the 1 hour observation interval in males at 2500 ppm (significant decreases in motor activity were recorded for high dose females during the 1 hour interval) vs controls. Additionally, high dose females showed significantly reduced forelimb grip strength vs controls. At 2500 ppm, group mean bodyweight gains were significantly decreased for treatment weeks 1 to 3 in males and weeks 1 to 2 in females vs controls and group mean bodyweights were significantly reduced for weeks 1 to 10 in males and throughout the treatment period for females. Group mean food consumption at the high dose level was significantly reduced for treatment weeks 1 to 4 (males) and 1 to 5 (females) vs controls (group mean food consumption was significantly increased for males at weeks 11 through 13). Statistically significant changes in group mean hematology results for both sexes at 2500 ppm included increased reticulocyte count, and decreases in hematocrit, hemoglobin concentration, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration vs controls. At 500 ppm, significant decreases were noted for group mean corpuscular volume and mean

corpuscular hemoglobin in both sexes, and for mean corpuscular hemoglobin concentration in males (reticulocytes were significantly increased in 500 ppm males) vs controls. Statistically significant changes in serum chemistry parameters included increased glutamic oxaloacetic transaminase and γ -glutamyl transpeptidase activities and decreases in calcium, sodium, and chloride in both sexes at the high dose level vs controls. At 500 ppm, significant decreases in group mean blood urea nitrogen in males and significant increases in total cholesterol in females were noted vs controls. At 2500 ppm, group mean relative organ weights (% of bodyweight) that were significantly increased compared to controls included liver, thyroid, kidney, spleen, lungs, and heart in both sexes (significant increases were also noted at 500 ppm for relative liver weights in both sexes and for kidney weights in males). Statistically significant incidences of macroscopic lesions were noted in the liver and thyroid at the high dose level and included dark color of liver (both sexes) and accentuated lobular pattern (males only) and thyroid hypertrophy (both sexes) compared to controls. Histopathology revealed statistically significant changes in liver, thyroid, kidney, pancreas, pituitary, adrenals, eye, spleen and bone marrow, testis, epididymis, ovaries, uterus, and vagina at 2500 ppm compared to controls. In liver, increases for both sexes were noted in centrilobular hepatocellular hypertrophy, periportal hepatocellular fatty change, and bile-duct hyperplasia (hepatocellular single cell necrosis was also increased for high dose females). Thyroid histology results included increased follicular cell hypertrophy and increased number of follicles (both sexes). In kidney, significant increases were noted for tubular basophilic change in both sexes and for glomerular mesangium thickening in females. In pancreas, acinar single cell necrosis was significantly increased in both sexes and decreased zymogene granules were noted for high dose males. Hypertrophy of anterior basophilic cells was significantly increased in pituitary of both sexes at the high dose level. Hypertrophy of zona fasciculata cells of the adrenal gland was significantly increased in both sexes at 2500 ppm. Retinal atrophy was significantly increased in the eyes of high dose females. In spleen, extramedullary hematopoiesis was significantly increased in both sexes (congestion/hyperemia was significantly increased for high dose females). In males, tubular atrophy of the testis and intra-ductal degenerated cells in the epididymis were significantly increased at 2500 ppm. In high dose females, atrophy of the ovary and uterus along with mucus-containing epithelial cells in the vagina were significantly increased. NOEL = 100 ppm (5.74 mg/kg/day (males) and 6.44 mg/kg/day (females)) based on increased liver weights, hematology changes. No adverse effect. Acceptable. (Green, 10/18/11).

Rat 28-Day Percutaneous Toxicity Study

**53161-0056 260973, "A 28-Day Percutaneous Toxicity Study of NNI-0101 in Rats", (S. Ishida, Gotemba Laboratory, Bozo Research Center Inc., Shizuoka, Japan, Project ID B6740, 27 May 2010). Ten CrI:CD(SD) Sprague-Dawley rats per sex per group were dermally treated (clipped, unabraded, semi-occluded) with NNI-0101 (pyrifluquinazon technical) (98.0%) at 0 (1% w/v aqueous carboxymethylcellulose sodium), 40, 200, and 1000 mg/kg/day for 4 weeks (6 hours per day, 5 days per week). No treatment-related effects were noted for the treatment sites, clinical signs, detailed observations, bodyweight, food consumption, ophthalmology, urinalysis, hematology, serum chemistry, organ weights, necropsy, or histology. Dermal and systemic NOEL = 1000 mg/kg/day. No adverse effect. Acceptable. (Green, 11/1/11).

Rat 28-Day Inhalation Toxicity Study

**53161-0055 260972, "NNI-0101: 28 Day Inhalation (Nose-only) Toxicity Study in the Rat", (D. A. Shaw, Covance Laboratories, Ltd., Harrogate, North Yorkshire, England, Covance Study No. 0608-079, July 2009). Ten CrI:CD(SD) rats per sex per group were exposed to NNI-0101 technical (pyrifluquinazon technical) (98.0%) by nose-only inhalation at 0 (air), 0.0419, 0.157, and 0.564 mg/l gravimetric means for 6 hours per day, 5 days per week for 4 weeks. Mass median aerodynamic diameters (MMAD) with the geometric standard deviations (GSDs) were 2.04 μ m MMAD (with a range of 1.16 to 3.21 μ m) and 2.20 GSD at 0.0419 mg/l; 2.61 μ m MMAD (with a

range of 1.60 to 3.38 μm) and 2.09 GSD at 0.157 mg/l; and 3.29 μm MMAD (with a range of 2.04 to 4.93 μm) and 2.17 GSD at 0.564 mg/l. One high dose female died on study day 25 due to toxicity and weakened condition from overnight fasting prior to blood sampling (consequently, feeding was restarted for high dose females and blood sampling was performed at necropsy (day 29) without fasting). Post-exposure observations in high dose animals surviving to scheduled necropsy included splayed gait, ataxia, palpebral closure, breathing irregularities, piloerection, and lethargy. Group mean bodyweight gain was significantly reduced at the high dose level for weeks 2 and 3 and overall (days 1 to 22 and days 1 to 29) for males and for days 1 to 22 for females vs controls. At the high dose level, group mean urine volume for both sexes was statistically increased and specific gravity decreased vs controls (increased urine volumes in high dose males indicated a significant dose response). Group mean absolute liver and lung weights (adjusted to overall mean necropsy bodyweight using analysis of covariance) were significantly increased for high dose males and females vs controls (kidney weights were also increased for high dose females and brain and thymus weights were decreased). Necropsy results were unremarkable. Histology results included increased centrilobular hypertrophy in liver (characterized by a centrilobular to panlobular distribution of hepatocytes with increased levels of pale eosinophilic staining cytoplasm) of mid dose (5 per sex) and all high dose animals compared to controls (0 incidence) and mitotic figures in liver were increased in 5 high dose females vs controls (0 incidence). In lung, the level of terminal airway inflammatory cells/alveolar macrophages was higher than controls in males at the mid dose level (5 vs 2) and in all animals of both sexes at the high dose level vs controls. NOEL (M/F) = 0.04 mg/l based on histological changes in liver and lungs. No adverse effect. Acceptable. (Green, 10/28/11).

Mouse 90-Day Dietary Toxicity Study

**53161-0050 260964, NNI-0101: Repeated Dose 90-Day Oral Toxicity Study in Mice (Dose Range-Finding Study for an 18-Month Carcinogenicity Study)", (M. Kuwahara, The Institute of Environmental Toxicology, Ibaraki, Japan, Study No. IET 03-0063, 21 September 2005). Ten ICR (Crj:CD-1) mice per sex per group received NNI-0101 technical (pyrifluquinazon technical) (98.0%) in the diet at 0 (basal diet), 60, 750, and 1500 ppm for 90 days. Group mean NNI-0101 intake was 7.58, 102.2, and 206 mg/kg/day for males and 9.13, 119, and 202 mg/kg/day for females at 60, 750, and 1500 ppm, respectively. All animals survived to scheduled sacrifice. No treatment related changes in clinical signs or bodyweights. Group mean food consumption was significantly decreased for high dose females during the treatment period (except for weeks 3 and 11) compared to controls. Group mean values for hematocrit, hemoglobin concentration, and erythrocyte count were significantly reduced for both sexes at the high dose level vs controls (hematocrit and hemoglobin concentration were also significantly reduced for mid dose females). Group mean glutamic oxaloacetic transaminase activity (GOT), glutamic pyruvic transaminase activity (GPT), γ -glutamyl transpeptidase activity (GGTP), and total bilirubin were significantly increased for both sexes at the high dose level vs controls (significant increases were also noted for alkaline phosphatase activity in high dose males and for GOT and GPT activity in mid dose males vs controls). Group mean relative liver, thyroid, and spleen weights were significantly increased in both sexes at 1500 ppm vs controls (additionally, increases in group mean relative weights were noted for adrenals in high dose males and for liver in both sexes at 750 ppm). Histopathology revealed significant increases in the incidence of hepatocellular focal necrosis, hepatocellular centrilobular hypertrophy, and cell infiltration in liver and follicular cell hypertrophy in the thyroid of both sexes at 1500 ppm (and in hepatocellular centrilobular hypertrophy in liver and follicular cell hypertrophy in the thyroid of both sexes at the mid dose level) vs controls. Significant increases in congestion and extramedullary hematopoiesis in spleen; diffuse cortical cell vacuolation and subcapsular cell hyperplasia in the adrenals; and interstitial cell hyperplasia in the testis were noted for high dose males vs controls. Atrophy of the ovary was significantly increased in high dose females. NOEL = 60 ppm (7.58 mg/kg/day for males and 9.13 mg/kg/day for females) based on liver weights and histology. No adverse effect. Acceptable. (Green, 12/19/11).

NEUROTOXICITY STUDIES

Rat Acute Oral Neurotoxicity Study

**53161-0074 260996, "Oral (Gavage) Acute Neurotoxicity Study of NNI-0101 Technical in Rats", (J.A. Foss, Charles River Laboratories, Horsham, PA., USA, Study No. DUU00002, 27 October 2006). Ten CrI:CD(SD) rats per sex per group were scheduled to receive a single oral gavage dose of NNI-0101 technical (pyrifluquinazon technical) (98.0%) at 0 (0.5% aqueous carboxymethylcellulose sodium), 100, 300, and 500 mg/kg. However, due to excess toxicity (one rat per sex at 300 mg/kg and 2 rats per sex at 500 mg/kg were sacrificed in moribund condition within 1 or 2 days after dosing) after the first 5 animals per sex per group were treated at 300 and 500 mg/kg, the remaining 5 per sex per group were reassigned to a fifth treatment group at 30 mg/kg. Loss of righting reflex was the only clinical sign that occurred in all rats sacrificed moribund at 300 and 500 mg/kg (additionally, at 300 and 500 mg/kg/day, a significant increase in the incidence of dehydration, decreased motor activity, prostration, ataxia, hyporeactivity, scant or no feces, hunched posture, coldness to touch, and lacrimation was noted for both sexes). All other animals survived to scheduled sacrifice. No treatment-related clinical signs were recorded at 30 and 100 mg/kg/day. In the functional observational battery (FOB), the incidence and severity of changes to sensorimotor reactivity, coordination, and autonomic processes (respiration and body temperature) were significantly increased in both sexes at 300 and 500 mg/kg 6 hours after dosing. No treatment-related alterations were noted at 300 and 500 mg/kg when surviving animals were examined at 7 and 14 days post dosing. Motor activity test (MA) results included, significant reductions (46% to 92% compared to controls) in cumulative values for both the number of movements and time spent in movement for both sexes at 300 and 500 mg/kg 6 hours after dosing (significant reductions were also noted for the first two 10 minute intervals). No treatment-related motor activity changes were noted for survivors at 7 and 14 days post treatment. Bodyweights were significantly decreased for males at 300 and 500 mg/kg for days 1 through 16 and for females on days 1 through 7 vs controls. Absolute food consumption values (g/day) were significantly reduced for males for days 1 through 16 and for females for days 1 through 4 at 300 and 500 mg/kg vs controls. Relative food consumption values (g/kg/day) were significantly decreased for both sexes for days 1 through 4 at 300 and 500 mg/kg and comparable or increased compared to controls thereafter. Neurohistology results for animals at scheduled sacrifice included: one control male with a single degenerating pyramidal neuron in the hippocampus; one 100 mg/kg female with minimal foci of nerve fiber degeneration within a section of the sciatic nerve and one per sex at 300 mg/kg with similar changes in the fibular (peroneal) nerve; one 300 mg/kg female with a focus of neuron degeneration within the medial frontal cerebral cortex (unilateral and associated with acute vascular degeneration (suggesting an ischemic pathogenesis)). None of the neurohistology results attained statistical significance compared to controls. Systemic NOEL = 100 mg/kg (bodyweights, FOB and MA results). No adverse effect. Acceptable. (Green, 1/23/12).

Rat 13-Week Dietary Neurotoxicity Study

**53161-0075 260997, "Oral (Diet) Subchronic Neurotoxicity Study of NNI-0101 Technical in Rats", (J. Foss, Charles River Laboratories, Preclinical Services, Horsham, PA., USA, Study No. DUU00004, 5 June 2009). Ten CrI:CD(SD) rats per sex per group received NNI-0101 (pyrifluquinazon technical) (98.0%) in the diet at 0 (basal diet), 30, 150, and 750 ppm for 13 weeks. Group mean daily intake of NNI-0101 technical during the treatment period was 1.8, 9.4, and 46.6 mg/kg/day for males and 2.2, 10.9, and 53.2 mg/kg/day for females at 30, 150, and 750 ppm, respectively. All animals survived to scheduled necropsy (except 1 mid dose male sacrificed on day 87 due to a broken palate and difficulty breathing). In the functional

observational battery (FOB), a significant increase in the number of rears in the open field was noted for high dose males during week 4 compared to controls (no concomitant increase in motor activity was recorded). In females at 750 ppm, significant reductions were noted for bodyweight (days 50 to 91) and bodyweight gain (days 1 to 8, 8 to 15, 15 to 22, 1 to 29, 29 to 57, and 1 through 91) vs controls (bodyweight gain was also significantly reduced in mid-dose females for days 29 to 57 and 1 through 91). Additionally, food consumption for high dose females was significantly reduced (absolute (g/day) and relative (g/kg/day) values, for days 1 to 8, 8 to 15 (and absolute values for days 15 to 22)) vs controls. No treatment-related changes were noted for clinical signs, ophthalmology, or motor activity. No treatment-related neurohistology changes were indicated. Systemic NOEL for males = 750 ppm (46.6 mg/kg/day) and for females = 30 ppm (2.2 mg/kg/day) based on bodyweight gain. Neurotoxicity NOEL = 750 ppm (46.6 mg/kg/day for males and 53.2 mg/kg/day for females). No adverse effect. Acceptable. (Green, 1/26/12).

IMMUNOTOXICITY STUDIES

Rat 4-Week Dietary Immunotoxicity Study

**53161-0082 261005, "4-Week Dietary T Cell-Dependent Antibody Assay with NNI-0101 in Rats", (J. Arrington, Covance Laboratories Inc., Madison, WI., USA., Covance Study No. 6238-110, August, 25, 2009). Ten CrI:CD(SD) rats per sex per group received NNI-0101 technical (pyrifluquinazon technical) (98.0%) in the diet at 0 (basal diet), 30, 150, and 750 ppm for 4 weeks. In the positive control group, 5 rats per sex received cyclophosphamide at 2.5 mg/ml by intraperitoneal injection once daily for 4 consecutive days prior to scheduled sacrifice. An agarose matrix plaque technique was used to assess the induction of the splenic anti-body forming cell (AFC) specific for the T cell-dependent antigen (SRBC). Each animal received a tail vein bolus injection of sheep red blood cells (SRBC) (2×10^8 cells per animal at 0.5 ml per animal) 4 days prior to sacrifice. Group mean test article consumption was 2.5 mg/kg/day (males) and 2.7 mg/kg/day (females) at 30 ppm; 11.9 mg/kg/day (males) and 13.0 mg/kg/day (females) at 150 ppm; and 61.8 mg/kg/day (males) and 63.1 mg/kg/day (females) at 750 ppm during the 4 week treatment period. All animals survived to scheduled necropsy. No treatment-related clinical signs were indicated. Group mean bodyweight gain was significantly decreased for treatment days 8 to 15 (both sexes), 15 to 22 (males), and 1 to 29 (females) vs controls. Group mean food consumption was significantly decreased for males at 150 and 750 ppm during treatment days 1 through 7. Necropsy results were unremarkable. No treatment-related effects on immune function were indicated. Positive controls were functional. Subacute NOEL = 150 ppm (11.9 mg/kg/day (males) and 13.0 mg/kg/day (females)) based on bodyweight gain. Immunotoxicity NOEL = 750 ppm (61.8 mg/kg/day (males) and 63.1 mg/kg/day (females)). Acceptable. (Green, 3/6/12).