CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
HUMAN HEALTH ASSESSMENT BRANCH
SUMMARY OF TOXICOLOGY DATA
Cyclaniliprole
Chemical Code # 6218, Document Processing Number (DPN) # 53314

14 April 2015

DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, no 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
Developmental toxicity, rat:	No data gap, no adverse effect
Developmental toxicity, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	No data gap, no adverse effect

Toxicology one-liners are attached.

All record numbers for the above study types through 280859 (53314-0025) were examined.
In the 1-liners below:
indicates an acceptable study. **Bold face indicates a possible adverse effect.
File name: T150414 prepared by R. Pan & P. Leung.

[1]Toxicology data for Cyclaniliprole have been submitted and reviewed as an insecticide.

This record contains summaries of studies. Individual worksheets may be useful for detailed assessment.

NEUROTOXICITY

Rat Acute Oral Neurotoxicity Study

**53314-0022 280853, "IKI-3106 Technical: Neurotoxicity Study by Oral Gavage Administration to Sprague-Dawley Rats followed by a 14-Day Observation Period" (M.J. Chapman, Huntingdon Life Sciences, Eye Research Centre, Eye, Suffolk, UK, Document No. JSM0262, May 31, 2012). Ten Sprague-Dawley Crl:CD®(SD) rats per sex per group received a single oral gavage dose of IKI-3106 technical (95.71% cyclaniliprole technical) at 0 (aqueous 1% w/v methylcellulose), 500, 1000, and 2000 mg/kg followed by a 14-day observation period. There were no treatment-related effects on clinical signs, mortality, bodyweight, food consumption, functional observation battery (FOB) and motor activity (MA) results, brain weight, brain measurements, gross pathology, or histology for treated groups compared to vehicle controls. Neurotoxicity was not indicated. Systemic NOEL (M & F) = 2000 mg/kg. Neurotoxicity NOEL (M & F) = 2000 mg/kg (no treatment-related effects at HDT). Acceptable. (Green, 2/20/15).

Rat Subchronic Dietary Neurotoxicity Study

**53314-0022 280854, "IKI-3106 Technical: Neurotoxicity Study by Dietary Administration to Sprague-Dawley Rats for 13 Weeks" (R.L. Allen, Huntingdon Life Sciences, Eye Research Centre, Eye, Suffolk, UK, Document No. JSM0311, November 8, 2012). Ten Sprague-Dawley Crl:CD®(SD) rats per sex per group received IKI-03106 technical (95.71% cyclaniliprole technical) in the diet at 0 (basal diet), 600, 3100, and 16000 ppm for 13 weeks. There were no treatment-related effects on clinical signs, mortality, bodyweight, food consumption, functional observation battery (FOB) and motor activity (MA) results, brain weight, brain measurements, gross pathology, or histology for treated groups compared to vehicle controls. Systemic NOEL = 16000 ppm (1085 mg/kg/day for males and 1279 mg/kg/day for females). Subchronic neurotoxicity NOEL (M & F) = 16000 ppm (no treatment-related effects at HDT). No adverse effect. Acceptable. (Green, 2/23/15).

IMMUNOTOXICITY

53314-0025 280859, "IKI-3106 Technical: 4 week dietary immunotoxicity study in the female CD-1 mouse"; 857; Crl:CD1(ICR) mice; Huntingdon Life Science Ltd., Huntingdon, Cambridgeshire, PE28 4HS, England. Document No. JSM0497, 9/23/2013; Coleman, D.; IKI-3106, Lot No.20101207, 95.71% (w/w) IKI-3106, a white crystalline solid, was administered to 10 female mice by diet at 0, 200, 1250 or 8000 ppm [mean test substance intake: 0, 34, 209, and 1352 mg/kg/day, respectively] (Groups 1, 2, 3 and 4, respectively) for 4 weeks. An additional group of 8 female mice (Group 5) were given control diet for 23 days followed with 20 mg/kg/day of cyclophosphamide via oral gavage for 5 consecutive days before euthanasia. All rats were administered 4 x 10^8 sRBC (sheep Red Blood Cells) via intravenous administration once 4 days before euthanasia (on day 25 of study). At the end of the 28-day treatment period, all rats were euthanized by carbon dioxide asphyxiation, and organ weights were measured. The splenocyte suspension was prepared and its viability was tested. The number of plaque-forming cells (PFC) present in the whole spleen was calculated. No mortality. No test substance treatment related changes in body weight, bodyweight gains, food consumption, organ weights and PFC were observed. Positive control group animals demonstrated decreased cells per spleen, decreased cells per million cells and decreased splenic plaque forming cells. **NOEL (No Observed Effect Level) for immunotoxicity: 8000 ppm (1352 mg/kg/day) in female mice after 4 weeks treatment. **Acceptable.** (Pan& Leung, 2/24/2015).

SUBCHRONIC STUDIES

Rat Subchronic Dietary Toxicity Study

53314-0011 280832, "IKI-3106 TGAI: Repeated dose 28-day oral toxicity study in rats"; supp; rat; The Institute of Environmental Toxicology, Ibaraki, 303-0043, Japan. Document No. IET 09-0141, 8/14/2010; Ohnuma, A.; IKI-3106 TGAI, Lot No. 0912-1, 97.15% (w/w) IKI-3106, a white solid. Groups of 6 male and 6 female rats were exposed to 0 (diet only), 300, 1250, 5000 or 20000 ppm test substance in diet (mean actual test substance intake: 26.4, 107, 426, and 1778 mg/kg/day for males of 300, 1250, 5000 and 20000 ppm groups, respectively; 26.4, 113, 443 and 1800 for females of 300, 1250, 5000 and 20000 ppm groups, respectively) for 28 days. No treatment related changes in body weight, food consumption, hematology, blood chemistry, urinalysis and necropsy were reported. **NOEL**: 20000 ppm (1778 mg/kg/day for males, 1800 mg/kg/day for females) due to no treatment related effects observed at HDT. **Supplemental** (Pan& Leung, 1/23/2015).

53314-0011 280833, "IKI-3106 TGAI: Repeated dose 90-day oral toxicity study in rats"; 821; Wistar rat; The Institute of Environmental Toxicology, Ibaraki, 303-0043, Japan. Document No. IET 09-0142, 5/6/2011; Ohnuma, A.; IKI-3106 TGAI, Lot No. 0912-1, 97.15% (w/w) IKI-3106, a white solid. Groups of 10 male and 10 female rats were exposed to 0 (diet only), 600, 6000 or 20000 ppm test substance in diet (mean actual test substance intake: 39.9, 402, and 1331 mg/kg/day for males of 600, 6000 and 20000 ppm groups, respectively; 43.3, 467 and 1594 for females of 600, 6000 and 20000 ppm groups, respectively) for 91 days. No mortality. No treatment related changes in body weight, food consumption, hematology, blood chemistry, urinalysis and necropsy were reported. Increased heart, liver and ovaries weights without accompanying histopathological changes were observed in the high dose group females. **NOEL: 20000 ppm (1331 mg/kg/day) for males, 6000 ppm (467 mg/kg/day) for females due to organ weight data in high dose group females. **Acceptable.** (Pan& Leung, 1/30/2015).

Rat Repeated Dosing 4-week Dermal Toxicity Study

**53314-0013 280836, "IKI-3106 Technical: Toxicity Study by Dermal Administration to Sprague-Dawley Rats for 4 Weeks" (P.B. Rees, Huntingdon Life Sciences, Eye Research Centre, Eye, Suffolk, UK, Project No. JSM0238, April 17, 2013). Ten Sprague-Dawley (Crl:CD®(SD)) rats per sex per group were dermally treated (clipped, intact, occluded skin) with IKI-3106 technical (95.71% cyclaniliprole) at 0 (purified water), 100, 300, and 1000 mg/kg/day 6 hours per day, 7 days per week for 4 weeks. No treatment-related effects were noted for clinical signs, dermal irritation, food consumption, bodyweight gain, ophthalmology, hematology, serum chemistry, urinalysis, organ weights, gross pathology, or histology. NOEL (M & F) = 1000 mg/kg/day (no effect at HDT). No adverse effect. Acceptable. (Green, 1/29/15).

Mouse Subchronic Dietary Toxicity Study

**53314-0016 280839, "IKI-3106 Technical: Preliminary carcinogenicity study by dietary administration to the CD-1 mouse for 13 weeks"; 821; Crl:CD1(ICR) mice; Huntingdon Life Science Ltd., Huntingdon, Cambridgeshire, PE28 4HS, England. Document No. JSM0163, 7/2/2012; O'Halloran, S.; IKI-3106 Technical, Lot No.20101207, 95.71% (w/w) IKI-3106, a white crystalline solid. Groups of 12 male and 12 female mice were exposed to 0 (diet only), 200,

1200 or 8000 ppm test substance in diet (mean actual test substance intake: 27, 159 and 1023 mg/kg/day for males of 200, 1200 and 8000 ppm groups, respectively; 34, 179 and 1350 for females of 200, 1200 and 8000 ppm groups, respectively) for 13 weeks. No mortality. No body weight, food consumption, hematology, blood chemistry, organ weights and necropsy that related to treatment were observed. **NOEL**: 8000 ppm (1023 mg/kg/day for males, 1350 mg/kg/day for females) due to no treatment related observations in high dose group animals. **Acceptable.** (Pan& Leung, 2/17/2015).

Dog Subchronic Dietary Toxicity Study

**53314-0012 280834, 280835, "IKI-3106 TGAI: Repeated Dose 90-Day Oral Toxicity Study in Dogs" (R. Ohtsuka, The Institute of Environmental Toxicology, Ibaraki, Japan, Laboratory Project ID: IET 11-0020, September 13, 2013, revised final report December 25, 2013). Four beagle dogs per sex per group received IKI-3106 TGAI (95.71% cyclaniliprole technical) in the diet at 0 (basal diet), 100, 1000, and 10000 ppm for 13 weeks. Group average test article intake during the study was 2.68, 26.8, and 266 mg/kg/day for males and 2.75, 26.9, and 270 mg/kg/day for females at 100, 1000, and 10000 ppm, respectively. There were no treatment-related effects on mortality, general and detailed clinical observations, bodyweight, food consumption, or urinalysis. Significant increases in group mean alkaline phosphatase activity were noted for males at 1000 ppm and for both sexes at 10000 ppm compared to controls at treatment weeks 7 and 13. At necropsy, 1 high dose male had an enlarged liver, and significant increases in group mean relative liver weights were noted for males at 100, 1000, and 10000 ppm vs controls. At histology, centrilobular hepatocellular hypertrophy was noted in the liver of 1 male at 10000 ppm. Record 280834 is a 28-day dietary toxicity study in beagle dogs. NOEL for males = 1000 ppm (26.8 mg/kg/day) based on liver histology. NOEL for females = 10000 ppm (270 mg/kg/day). Adverse effects were not indicated. Acceptable. (Green, 1/28/15).

53314-0012 280834, "IKI-3106 TGAI: Repeated dose 28-Day Oral Toxicity Study in Dogs" (T. Yoshida, The Institute of Environmental Toxicology, Ibaraki, Japan, Laboratory Project ID: IET 10-0113, September 13, 2013). One beagle dog per sex per group received IKI-3106 TGAI (95.71% cyclaniliprole technical) in the diet at 0 (basal diet), 100, 1000, 10000, and 30000 ppm for 28 days. Average test article intake during the study was 3.08, 27.3, 288, and 1035 mg/kg/day for males and 3.20, 32.2, 309, and 1032 mg/kg/day for females at 100, 1000, 10000, and 30000 ppm, respectively. No treatment-related changes were noted for mortality, general and detailed clinical observations, food consumption, ophthalmology, urinalysis, or hematology. Cumulative bodyweight gain for both sexes at 30000 ppm was lower than that for the controls. Treatment-related liver weight increases were noted for absolute and relative weights of the male at 1000 ppm and of both sexes at 10000 ppm, and for relative weights of both sexes at 30000 ppm vs the controls. The alkaline phosphatase activity value at the end of treatment for the 10000 ppm female was higher than for the other female groups including the control. At histology, slight centrilobular hepatocellular hypertrophy was noted in the liver of the 10000 ppm male. Supplemental data. (Green, 1/27/15). No worksheet.

METABOLISM STUDIES

Metabolism, Rat

**53314-0023 280855, "IKI-3106: Metabolism in rats"; 851; Crl:CD1(ICR) mice; Huntingdon Life Science Ltd., Huntingdon, Cambridgeshire, PE28 4HS, England. Document No. JSM0497, 10/22/2013; Penketh, S.; [^{14}C-Ph]-IKI-3106, Lot No.CP-3560, specific activity: 5.00 MBq/mg,

>97% radiochemical purity; [^{14}C-Pz]-IKI-3106, Lot No.CP-3561, specific activity: 3.30 MBq/mg, >97% radiochemical purity, IKI-3106, Lot Number 20090723, 99.45% pure, was administered to male and female Wistar rats by oral gavage at 10 mg/kg ([^{14}C-Ph]-IKI-3106 or [^{14}C-Pz]-IKI-3106), 400 mg/kg [^{14}C-Ph]-IKI-3106 single oral doses or 10 mg/kg ([^{14}C-Ph]-IKI-3106 or [^{14}C-Pz]-IKI-3106) for 14 daily oral doses. Excretion and retention of radioactivity in urine, feces, cagewash, expired air and carcass were measured. Majority of radioactivity (>90% of dose) was detected in feces within 72 hours after dosing. Tissue distribution of radioactivity was measured. Carcass, plasma, whole blood and skeletal muscle had the highest radioactivities at 168 hours after dose. Repeated dosing resulted in accumulated radioactivity in carcass at 168 hours after day 14 dose. Carcass, plasma, whole blood and skeletal muscle had the highest radioactivities at 168 hours after day 14 dose. Absorption of the test substance was examined by dosing the bile duct cannulated rats at10 or 400 mg/kg [^{14}C-Ph]-IKI-3106 single dose. Majority of radioactivity (near or >90% of dose) was detected in feces within 48 hours after dosing. Absorbed radioactivity counted for near or less than 10% of dose for 10 mg/kg group, less than 5% for the 400 mg/kg group. Mean blood or plasma radioactivity after 10 or 400 mg/kg [^{14}C-Ph]-IKI-3106 reached high level at 24 hours after dose, there was not enough reduction till the end of the 120 or 168 hour observation period for determination of $T_{1/2}$. Plasma and whole blood radioactivity after repeated dose of 10 mg/kg [^{14}C-Ph]-IKI-3106 reached peak at 3 hours after day 14 dose. The peak effect lasted through 72 hours after day 14 dose, with slight reduction at 168 hours after day 14 dose. Metabolites identified were NSY-28, from plasma, kidneys, liver and fat; YT-1284 and NSY-27 were found mainly in liver at smaller amounts; unchanged test substance was identified in feces, liver, fat, kidney and plasma. **Acceptable.** (Pan& Leung, 3/6/2015).

SB950-MANDATED HEALTH EFFECTS STUDIES

Chronic Toxicity, Rat

53314-0014 280837, “IKI-3106 TGAI: Repeated dose 1-year oral toxicity study in rats”; 831; Wistar rat; The Institute of Environmental Toxicology, Ibaraki, 303-0043, Japan. Document No. IET 10-0114, 3/8/2013; Koyama, A.; IKI-3106 TGAI, Lot No. 20101207, 95.71% (w/w) IKI-3106, a white solid. Groups of 21 male and 21 female rats were exposed to 0 (diet only), 200, 2000, 6000 or 20000 ppm test substance in diet (mean actual test substance intake: 9.21, 89.6, 277 and 955 mg/kg/day for males of 200, 2000, 6000 and 20000 ppm groups, respectively; 11.7, 117, 358, and 1213 for females of 200, 2000, 6000 and 20000 ppm groups, respectively) for 52 weeks. One 20000ppm group female was sacrificed on week 25 due to human error. Another female of the same dose level was found dead at week 28. Necropsy revealed bile calculi formation with luminal dilatation in the common bile duct. No body weight, food consumption changes that related to treatment were observed. Hematology, blood chemistry, urinalysis, organ weights and necropsy revealed no treatment related effects. **NOEL: 20000 ppm (955 mg/kg/day for males, 1213 mg/kg/day) for females due no treatment related effects at HTD. **Acceptable.** (Pan& Leung, 2/2/2015).

Chronic Toxicity, Dog

**53314-0015 280838, “IKI-3106 TGAI: Repeated Dose 1-Year Oral Toxicity Study in Dogs” (R. Ohtsuka, The Institute of Environmental Toxicology, Ibaraki, Japan, Laboratory Project ID: IET 11-0021, November 26, 2013 (Revised Final Report on December 24, 2013)). Four beagle dogs per sex per group received IKI-3106 TGAI (95.71% cyclaniliprole technical) in the diet at 0 (basal diet), 50, 150, 1000, and 10000 ppm for 1 year. Group average test article intake during the study was 1.29, 4.07, 27.2, and 259 mg/kg/day for males and 1.47, 4.20, 27.6, and 288

mg/kg/day for females at 50, 150, 1000, and 10000 ppm, respectively. Significant increases in group mean alkaline phosphatase activity were noted for both sexes at 10000 ppm at weeks 13, 26, and 52 and for both sexes at 150 and 1000 ppm at week 52 compared to controls. Group mean relative liver weights were significantly increased for both sexes at 1000 and 10000 ppm and for females at 50 and 150 ppm compared to controls. Group mean absolute liver weights were also significantly increased for both sexes at 10000 ppm. At histology, centrilobular hepatocellular hypertrophy was noted in the liver of 1 male and 1 female at 10000 ppm. NOEL (M & F) = 1000 ppm (27.2 mg/kg/day for males and 27.6 mg/kg/day for females) based on liver histology. Adverse effects were not indicated. Acceptable. (Green and Leung, 1/30/15).

Oncogenicity, Rat

**53314-0018 280841, "IKI-3106 TGAI: Carcinogenicity study in rats"; 832; Wistar rat; The Institute of Environmental Toxicology, Ibaraki, 303-0043, Japan. Document No. IET 10-0115, 12/6/2013; Ohtsuka, R.; IKI-3106 TGAI, Lot No. 20101207, 95.71% (w/w) IKI-3106, a white solid. Groups of 51 male and 51 female rats were exposed to 0 (diet only), 200, 2000, 6000 or 20000 ppm test substance in diet (mean actual test substance intake: 7.93, 82.5, 249 and 834 mg/kg/day for males of 200, 2000, 6000 and 20000 ppm groups, respectively; 10.3, 103, 306 and 1041 for females of 200, 2000, 6000 and 20000 ppm groups, respectively) for 104 weeks. Final mortality: 15/9, 13/11, 9/7, 9/14 and 5/15 for 200, 2000, 6000 and 20000 ppm group males/females, respectively. No body weight, food consumption changes that related to treatment were observed. Hematology, organ weights and necropsy revealed no treatment related effects. Increased thyroid follicular cell hypertrophy was observed in 20000ppm group males at terminal kill. NOEL: 6000 ppm for males (249 mg/kg/day for males) due to histopathological findings, 20000ppm (1041 mg/kg/day) for females due no treatment related effects at HTD. Acceptable. (Pan& Leung, 2/6/2015).

Oncogenicity, Mouse

53314-0017 280840, "IKI-3106 Technical: Preliminary carcinogenicity study by dietary administration to the CD-1 mouse for 78 weeks"; 821; Crl:CD1(ICR) mice; Huntingdon Life Science Ltd., Huntingdon, Cambridgeshire, PE28 4HS, England. Document No. JSM0163, 10/15/2013; Chase, K.; IKI-3106, Lot No.20101207, 95.71% (w/w) IKI-3106, a white crystalline solid. Groups of 51 male and 51 female mice were exposed to 0 (diet only), 200, 1250 or 8000 ppm test substance in diet (mean actual test substance intake: 22.7, 140 and 884 mg/kg/day for males of 200, 1250 and 8000 ppm groups, respectively; 31.6, 186 and 1316 for females of 200, 1250 and 8000 ppm groups, respectively) for 78 weeks. No treatment related effects on mortality, body weight, food consumption, hematology, blood chemistry, organ weights and necropsy were observed. **NOEL: 8000 ppm (884 mg/kg/day for males, 1316 mg/kg/day for females) due to no treatment related observations in high dose group animals. **Acceptable.** (Pan& Leung, 2/19/2015).

Reproduction, Rat

**53314-0020 280846, 280847, "Two-Generation Reproductive Toxicity Study of IKI-3106 TGAI in Rats" (S. Fujii, Safety Research Institute for Chemical Compounds Co., Ltd.; Sapporo, Japan; Study No. SR11274, September 24, 2013). Twenty-four F0 and F1 Crl:CD (SD) rats per sex per group received IKI-3106 TGAI (95.71% cyclaniliprole technical) in the diet at 0 (basal diet), 500, 3000, and 20000 ppm through 2 generations with 1 litter per generation. Group mean test article intake during the study for F0 parents was 32.6, 193.6, and 1311 mg/kg/day for males and 40.5, 237.4, and 1658 mg/kg/day for females, and the values for F1 parents were 37.8, 224.3, and 1543 mg/kg/day for males and 45.5, 269.9, and 1829 mg/kg/day for females at 500, 3000, and 20000 ppm, respectively. There were no treatment-related effects for F0 and F1

parental male and female clinical signs, mortality, bodyweight, bodyweight gain, food consumption, necropsy results, organ weights, histology results, copulation or fertility indices in both sexes, gestation and delivery indices, and number of implantations in females, sperm parameters in males, or sexual development (F1 males and females) at 500, 3000, and 20000 ppm compared to controls. No treatment-related effects were noted for F1a and F2a pup clinical signs, mortality, numbers of pups delivered, sex ratios, viability and lactation indices, pup weights, physical development, reflex responses, necropsy, or organ weights at 500, 3000, or 20000 ppm compared to controls. Record 280846 is a dose-range finding study for the main study. Parental, Pup, and Reproductive NOEL (M & F) = 20000 ppm (1311 mg/kg/day (FO males), 1543 mg/kg/day (F1 males), and 1658 mg/kg/day (F0 females) and 1829 mg/kg/day (F1 females)). No adverse effect. Acceptable. (Green and Leung, 2/18/15)

53314-0020 280846, "Two-Generation Reproductive Toxicity Study of IKI-3106 TGAI, Dose-Range Finding Study" (S. Fujii, Safety Research Institute for Chemical Compounds Co., Ltd.; Sapporo, Japan; Study No. SR11273; September 13, 2012). Eight F0 Crl:CD (SD) rats per sex per group received IKI-3106 TGAI (95.71% cyclaniliprole technical) in the diet at 0 (basal diet), 600, 2000, 6000, and 20000 ppm through 1 generation with 1 litter. Group mean F0 test article intake during the treatment period was 37.4, 118, 376, and 1270 mg/kg/day for males and 53.9, 176, 529, and 1788 mg/kg/day for females at 600, 2000, 6000, and 20000 ppm, respectively. There were no treatment-related effects on mortality, clinical signs, bodyweight, bodyweight gain, food consumption, gross pathology, or organ weights of F0 parental male and female treated groups compared to controls. No treatment-related findings were noted for the copulation or fertility index in F0 males; or estrous cycles, fertility index, gestation or delivery index, gestation length, or number of implantations in F0 females at 600, 2000, 6000, and 20000 ppm compared to controls. No treatment-related effects were noted for clinical signs, mortality, bodyweights, number of pups delivered, sex ratio, viability index, necropsy findings, or organ weights of F1 pups at 600, 2000, 6000, and 20000 ppm compared to controls. Parental and pup NOEL = 20000 ppm (no treatment-related effects at HDT, 1270 mg/kg/day for males and 1788 mg/kg/day for females). Supplemental data. (Green, 2/6/15). No worksheet.

Teratology, Rabbit

**53314-0019 280844, 280845, "IKI-3106 TGAI: Teratogenicity Study in Rabbits" (K. Takahashi, The Institute of Environmental Toxicology, Ibaraki, Japan, Laboratory project ID: IET 11-0025, February 18, 2013). Twenty-five artificially inseminated female Japanese White rabbits (Kbl:JW) per group received IKI-3106 TGAI (95.71% cyclaniliprole technical) at 0 (aqueous 1% sodium carboxymethylcellulose), 100, 300, and 1000 mg/kg/day on gestation days 6 to 27. There were no treatment-related effects on maternal clinical signs, bodyweights, bodyweight gain, food consumption, or gross pathology at any treatment level compared to controls. No treatment-related effects were noted for mean gravid uterine weights, mean numbers of corpora lutea and implants, or percent incidence of preimplantation losses at 100, 300, and 1000 mg/kg/day compared to controls. There were no treatment-related effects on mean numbers of live fetuses, fetal resorptions, fetal deaths, fetal sex ratios, mean fetal weights, or findings from fetal external, visceral, and skeletal examinations at 100, 300, and 1000 mg/kg/day compared to controls. Record 280844 is a rabbit dose range-finding teratogenicity study. Maternal NOAEL = 1000 mg/kg/day. Developmental NOAEL = 1000 mg/kg/day. No adverse effect. Acceptable. (Green and Leung, 2/5/15).

53314-0019 280844, "IKI-3106 TGAI: Dose Range-Finding Teratogenicity Study in Rabbits" (H. Hojo, The Institute of Environmental Toxicology, Ibaraki, Japan, Laboratory project ID: IET 11-0024, October 17, 2011). Eight artificially inseminated female Japanese White rabbits

(Kbl:JW) received IKI-3106 TGAI (95.71% cyclaniliprole technical) by oral gavage at 0 (aqueous 1% sodium carboxymethyl cellulose), 30, 100, 300, and 1000 mg/kg/day on gestation days 6 to 27. No treatment-related maternal effects were noted for mortality, bodyweights, bodyweight gains, food consumption, or gross pathology at any treatment level compared to controls. There were no treatment-related effects on mean gravid uterine weights, mean numbers of corpora lutea and implants, and percent incidence of preimplantation losses in the treated dams compared to controls. Group mean numbers of live fetuses and percentage incidences of resorptions and fetal deaths at 30, 100, 300, and 1000 mg/kg/day were comparable to vehicle control values. Fetal sex ratios, mean fetal weights, mean placental weights, and external evaluations of live fetuses at 0, 30, 100, 300, and 1000 mg/kg/day were all comparable. Maternal and developmental NOEL = 1000 mg/kg/day. Supplemental data (Green, 2/5/15). No worksheet.

Teratology, Rat

**53314-0019 280842, 280843, "IKI-3106 TGAI: Teratogenicity Study in Rats" (K. Takahashi, The Institute of Environmental Toxicology, Ibaraki, Japan, Laboratory project ID: IET 11-0023, September 24, 2012). Twenty-four sperm positive female Wistar Hannover (BrlHan:WIST@Jcl[GALAS]) rats per group received IKI-3106 TGAI (95.71% cyclaniliprole technical) by oral gavage at 0 (aqueous 1% sodium carboxymethylcellulose), 100, 300, and 1000 mg/kg/day on gestation days 6 to 19. There were no treatment-related effects on maternal clinical signs, bodyweights, bodyweight gain, food consumption, or gross pathology at any treatment level compared to controls. No treatment-related effects were noted for mean gravid uterine weights, mean numbers of corpora lutea and implants, or percent incidence of preimplantation losses at 100, 300, and 1000 mg/kg/day compared to controls. There were no treatment-related effects on mean numbers of live fetuses, fetal resorptions, fetal deaths, fetal sex ratios, mean fetal weights, or findings from fetal external, visceral, and skeletal examinations at 100, 300, and 1000 mg/kg/day compared to controls. Record 280842 is a rat dose range-finding teratogenicity study. Maternal NOAEL = 1000 mg/kg/day. Developmental NOAEL = 1000 mg/kg/day. No adverse effect. Acceptable. (Green and Leung, 2/4/15).

53314-0019 280842, "IKI-3106 TGAI: Dose Range-Finding Teratogenicity Study in Rats" (K. Takahashi, The Institute of Environmental Toxicology, Ibaraki, Japan, Laboratory project ID: IET 11-0022, January 25, 2012). Eight sperm-positive female Wistar Hannover (BrlHan:WIST@Jcl[GALAS]) rats received IKI-3106 TGAI (95.71% cyclaniliprole technical) by oral gavage at 0 (aqueous 1% sodium carboxymethylcellulose), 30, 100, 300, and 1000 mg/kg/day on gestation days 6 to 19. No treatment-related maternal effects were noted for mortality, bodyweights, bodyweight gains, food consumption, or gross pathology at any treatment level compared to controls. All dams in the vehicle control and treatment groups were pregnant. There were no treatment-related effects on mean gravid uterine weights, mean numbers of corpora lutea and implants, and percent incidence of preimplantation losses in the treated dams compared to controls. Group mean numbers of live fetuses and percentage incidences of resorptions and fetal deaths at 30, 100, 300, and 1000 mg/kg/day were comparable to vehicle control values. Fetal sex ratios, mean fetal weights, mean placental weights, and external evaluations of live fetuses at 0, 30, 100, 300, and 1000 mg/kg/day were all comparable. Maternal and developmental NOEL = 1000 mg/kg/day. Supplemental data. (Green, 2/3/15). No worksheet.

Bacteria reverse mutation test

53314-0021,** 280848 "IKI-3106 TGAI: Bacteria reverse mutation test", 842, Bacteria reverse

mutation assay. Matsumoto, K., The Institute of Environmental Toxicology, Ibaraki, 303-0043, Japan. 6/29/2011. Doc. No. IET 10-0116. IKI-3106 TGAI, Lot No. 20101207, 95.71% (w/w) IKI-3106, a white solid. Test substance up to 5000 (Dose-range finding assay and mutation assay) ug/plate in DMSO was tested in *Salmonella Typhimurium* TA 1535, TA1537, TA100, TA98 and *Escherichia Coli* WP_2uvrA for potential mutagenicity with or without metabolic activation of rat liver S9-mix. Strain specific positive control materials induced expected responses in both assays with or without metabolic activation. Test substance showed negative responses over the dose range tested in all tester strains, with or without metabolic activation. The test substance is not mutagenic. Acceptable. (Pan & Leung, 2/9/2015)

**53314-0021, 280849 "NK-1375, a degradate of IKI-3106 TGAI: Bacteria reverse mutation test", 842, Bacteria reverse mutation assay. May, K., Huntington Life Sciences, Eye, Suffolk, UK. 5/22/2012. Doc. No. JSM0278. NK-1375, Lot No. 233-004-22-3, 98.6% (w/w) NK-1375, a powder. Test substance up to 5000 (mutation assay) ug/plate in DMSO was tested in *Salmonella Typhimurium* TA 1535, TA1537, TA100, TA98 and *Escherichia Coli* WP_2uvrA for potential mutagenicity with or without metabolic activation of rat liver S9-mix. Strain specific positive control materials induced expected responses in both assays with or without metabolic activation. Test substance showed negative responses over the dose range tested in all tester strains, with or without metabolic activation. The test substance is not mutagenic. Acceptable. (Pan & Leung, 2/9/2015)

Gene Mutation

**53314-0021, 280850 "IKI-3106 TGAI: Gene mutation test in mouse lymphoma cells", 842, In vitro mammalian cell gene mutation assay. Matsumoto, K., The Institute of Environmental Toxicology, Ibaraki, Japan. 3/14/2012. Doc. No. IET 10-0119. IKI-3106 TGAI, Lot No. 20101207, 95.71% (w/w) IKI-3106, white solid. Test substance up to 320 ug/ml in DMSO was tested for potential mutagenicity for 3 and 24 hours with or without metabolic activation of rat liver S9-mix. Positive control materials induced expected responses with or without metabolic activation. Test substance showed negative responses over the dose range tested in all test conditions with or without metabolic activation. The test substance is not mutagenic. Acceptable. (Pan & Leung, 2/10/2015)

53314-0021,** 280850 "IKI-3106 TGAI: Gene mutation test in mouse lymphoma cells", 842, In vitro mammalian cell gene mutation assay. Matsumoto, K., The Institute of Environmental Toxicology, Ibaraki, Japan. 3/14/2012. Doc. No. IET 10-0119. IKI-3106 TGAI, Lot No. 20101207, 95.71% (w/w) IKI-3106, white solid. Test substance up to 320 ug/ml in DMSO was tested for potential mutagenicity for 3 and 24 hours with or without metabolic activation of rat liver S9-mix. Positive control materials induced expected responses with or without metabolic activation. Test substance showed negative responses over the dose range tested in all test conditions with or without metabolic activation. The test substance is not mutagenic. **Acceptable.** (Pan & Leung, 2/10/2015)

Chromosome Effects

53314-0021,** 280851 "IKI-3106 TGAI: Chromosome aberration test in cultured mammalian cells", 842, mammalian chromosome aberration test. Wada, K., The Institute of Environmental Toxicology, Ibaraki, Japan. 6/2/2011. Doc. No. IET 10-0117. IKI-3106 TGAI, Lot No. 20101207, 95.71% (w/w) IKI-3106, white solid. Test substance up to 320 ug/ml in DMSO was tested for potential mutagenicity in Chinese hamster CHL/IU cells for 6 hours with or without metabolic activation of rat liver S9-mix, at 78.1-625 ug/ml; or for 24 and 48 continuous treatments without S-9 mix, at 19.5-313 ug/ml and at 15.4-78.1 ug/ml, respectively. Chromosome preparations were made after 18 hours incubation following the 6-hour short-term treatment. Positive control

materials induced chromosome aberrations with or without metabolic activation. Test substance showed negative responses over the dose range tested in all test conditions with or without metabolic activation. The test substance is not mutagenic. **Acceptable.** (Pan & Leung, 2/12/2015)

Micronucleus test in mice

53314-0021,** 280852 "IKI-3106 TGAI: micronucleus test in mice", 842, bone marrow micronucleus test. Wada, K., The Institute of Environmental Toxicology, Ibaraki, Japan. 6/28/2011. Doc. No. IET 10-0118. IKI-3106 TGAI, Lot No. 20101207, 95.71% (w/w) IKI-3106, white solid. Test substance at 500, 1000 or 2000 mg/kg was administered to 5 male mice/dose level, bone marrow smears were prepared 24 or 48 (vehicle and high dose group only) hours later. In addition, vehicle control group (0.5% Methylcellulose) and positive control group (0.5 mg/kg Mitomycin) containing 5 male mice was dosed in similar manner. The mice were euthanized 24 or 48 hours after dose, bone marrow smears were prepared and micronucleated polychromatic erythrocytes were counted. Positive control materials induced statistically significant increase of percentage of micronucleated polychromatic erythrocytes. Test substance showed negative responses over the dose range tested at 24 or 48 hours after administration. The test substance is not mutagenic. **Acceptable.** (Pan & Leung, 2/17/2015)