SUMMARY OF TOXICOLOGY DATA
Pyriofenone

Chemical Code # 6156, Document Processing Number (DPN) 53251
SB 950 # NA
1/20/15

DATA GAP STATUS

<table>
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<tr>
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Toxicology one-liners are attached.

All record numbers for the above study types through 278828 (Document No. 53251-0035) were examined. This includes all relevant studies indexed by DPR as of 1/20/15.

In the 1-liners below:
- indicates an acceptable study.
- Bold face indicates a possible adverse effect.
- ## indicates a study on file but not yet reviewed.

File name: T150120
Revised by T. Moore, 1/20/15
NOTE: The following symbols may be used in the Table of Contents which follows:

* = data adequately address FIFRA requirement
† = study(ies) flagged as “possible adverse effect”
N/A = study type not currently required

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

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METABOLISM AND PHARMACOKINETICS
53251-0032; 278825; “IKF-309: Metabolism in Rats”; (L.J.L. Knight; Huntingdon Life Sciences Ltd., Alconbury, Huntingdon, PE28 4HS, England; Project ID No. ISK0281; 4/21/09, amended, 2/19/10); Fischer 344 rats of both sexes were dosed with either 14C-(phenyl)-IKF-309 (batch no. EPPS-06-045-73-18 (CP-3098), specific activity 6.22 MBq/mg, radiochemical purity: >97%) or 14C-(pyridyl)-IKF-309 (batch no. CP-3097, specific activity: 4.75 MBq/mg, radiochemical purity: >97%). The specific activity of the dosing preparations was adjusted with the addition of non-radiolabeled IKF-309 (batch no. 0608, purity: 99.19%). Four studies were performed; excretion balance, bile duct cannulation, pharmacokinetic, and tissue distribution. In the excretion balance study, 4 animals/sex/group were dosed orally by gavage with 5 or 200 mg/kg of either radiolabeled test material. Urine and fecal samples were collected at various time points up to 5 days post-dose. In the repeated dose excretion balance study, 4 animals/sex were dosed orally with 5 mg/kg/day of 14C-(phenyl)-IKF-309 for 14 days. Urine and feces samples were collected on days 2 and 8 of dosing and up to 120 hours post-final dose. In the bile duct cannulation study, 5 bile duct-cannulated rats/sex/group were dosed with 5 or 200 mg/kg of either radiolabeled test material and bile, urine and fecal samples were collected for up to 48 hours post-dose. In the pharmacokinetic study, 12 animals/sex/group received a single dose of 5 or 200 mg/kg of either test material. Blood samples were collected at specified intervals up to 5 days post-dose. A repeated dose pharmacokinetic study was performed in which 12 animals/sex were dosed orally with 5 mg/kg/day of 14C-(phenyl)-IKF-309 for 14 days. Blood was drawn from specified cohorts of animals before dosing on days 3, 5, 10 and 14 and at specified intervals up to 120 hours post-final dose. In the tissue distribution study, 9 animals/sex/group were dosed orally by gavage with 5 or 200 mg/kg of either test material. Three animal/sex/group/time point were euthanized at specified time points post-dose based upon the pharmacokinetic parameters. Distribution of radiolabel was also assessed in the tissues of the animals in the excretion balance study at 120 hours post-dose. Excretion of radiolabel via the urine represented 11 to 20% of the administered dose for the 5 mg/kg treatment level and 6 to 9% for the 200 mg/kg group. Seventy three to 89% of the radiolabel was recovered in the feces at 5 mg/kg, increasing to 85 to 91% at 200 mg/kg. The multiple dosing regimen did not alter this profile. In the bile duct- cannulation study, the radiolabel in the bile ranged from 65 to 81% of the administered dose at 5 mg/kg and 32 to 49% of the dose at 200 mg/kg. For the 5 mg/kg treatment group, the total absorbed dose ranged from 76% to 89%. For the 200 mg/kg group, absorption was reduced to 36 to 53% of the administered dose. For the intraduodenal administration study, the profile was quite similar. In the pharmacokinetic study, the plasma Cmax level for the 5 mg/kg group ranged from 0.58 to 0.88 µg equivalents/g, increasing to 0.771
to 1.236 µg equivalents/g after treatment for 14 days. The time at which the maximal plasma levels (Tmax) were achieved ranged between 4 and 24 hours regardless of the treatment levels. For the multiple treatment regimen, the Tmax appeared to plateau between 1 and 12 hours post-final dose for the males and was 12 hours for the females. The terminal half-lives (T\textsubscript{1/2}) of radiolabel in the plasma ranged from 12.8 to 46.1 hours irrespective of the dosing regimen. In the tissue distribution study, the only tissues/organs which had a tissue: plasma ratio >1 for all of the treatment regimens were the liver, kidneys, and gastrointestinal tract and contents. The females had a ratio of >1 for the abdominal fat at 48 and/or 72 hours post-dose for both radiolabeled test materials at the two treatment levels. The females treated with 200 mg/kg of \textsuperscript{14}C-(pyridyl)-IKF-309 also demonstrated tissue: plasma ratios of >1 for the ovaries, uterus, bone marrow, whole blood and blood cells at 72 hours post-dose. Urine, feces and bile which were collected in the excretion balance and bile cannulation studies were analyzed for metabolites. Hydroxylation accompanied by secondary glucuronidation was the primary path of metabolism. **Study acceptable.** (Moore, 11/4/14)

**GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT**

**Acute oral toxicity, rat**

53251-0013; 278791; “IKF-309 Technical: Acute Oral Toxicity to the Rat (Acute Toxic Class Method)”; (E.L. Moore; Huntington Life Sciences Ltd., Alconbury, Huntingdon, Cambridgeshire, PE28 4HS England; Project ID No. ISK0313; 5/14/08); Six female CD rats were dosed orally by gavage with 2000 mg/kg of IKF-309 technical (lot no. 0701, purity: 97.88%) (vehicle: aqueous 1% (w/v) methylcellulose). No deaths resulted from the treatment. Two animals demonstrated abnormal body position shortly after dosing, clearing by 5 hours post-dose. No treatment-related lesions were noted in the necropsy examination. LD\textsubscript{50} (F) > 2000 mg/kg; Toxicity Category III; **Study acceptable.** (Moore, 9/11/14)

**Acute dermal toxicity**

53251-0013; 278292; “IKF-309 Technical: Acute Dermal Toxicity to the Rat”; (E.L. Moore; Huntington Life Sciences Ltd., Alconbury, Huntingdon, Cambridgeshire, PE28 4HS England; Project ID No. ISK0312; 3/17/08); The skin of 5 CD (Crl:CD BR) rats/sex was exposed to 2000 mg/kg of IKF-309 Technical (lot no. 0701; purity: 97.88%) for 24 hours under an occlusive wrap. No deaths resulted from the treatment. Very slight erythema was noted at the site of application, resolving by day 7. No treatment-related lesions were noted in the necropsy examination. LD\textsubscript{50} (M/F) > 2000 mg/kg; Toxicity Category III; **Study acceptable.** (Moore, 9/11/14)

**Acute inhalation toxicity, rat**

53251-0013; 278793; “IKF-309 Technical: An Acute (4-Hour) Inhalation Toxicity Study in the Rat Via Nose-Only Exposure (Amended)”; (G.M. Hoffman; Eurofins/Product Safety Laboratories, Dayton, NJ under the aegis of Huntington Life Sciences, East Millstone, NJ; HLS Study No. 07-6318 (EPSL Study No. 23566); 9/8/08); Five Sprague-Dawley rats/sex were exposed nose-only to 5.18 mg/l (gravimetric) of IKF-309 Technical (lot no. 0701; purity: 97.88%) for 4 hours. The mean MMAD (GSD) was 3.90 (2.18) µm. No deaths resulted from the exposure. Nasal discharge was noted for 3 animals immediately after the exposure. Otherwise no treatment-related clinical signs were noted. No treatment-related lesions were evident in the necropsy examination. LC\textsubscript{50} (M/F) > 5.18 mg/l; Toxicity Category IV; **Study acceptable.** (Moore, 9/12/14)
Primary eye irritation, rabbit

53251-0013; 278794; “IKF-309 Technical: Eye Irritation Study to the Rabbits”; (P. Rees; Huntingdon Life Sciences Ltd., Alconbury, Huntingdon, Cambridgeshire, PE28 4HS England; Project ID No. ISK0314; 8/27/14); The eyes of 3 New Zealand White rabbits were treated by ocular instillation with 0.1 ml (approx. 100 mg)/eye of IKF-309 Technical (lot no. 0701; purity: 97.88%). No corneal opacity nor iritis were evident throughout the 72-hour observation period. Conjunctival redness, grade 1 (1/3) was noted at 24 hours post-dose, clearing by 48 hours. No chemosis nor discharge were evident at 24 hours post-dose and thereafter. Toxicity Category IV; Study acceptable. (Moore, 9/12/14)

Primary dermal irritation

53251-0013; 278795; “IKF-309 Technical: Skin Irritation Study to the Rabbits”; (P. Rees; Huntingdon Life Sciences Ltd., Alconbury, Huntingdon, Cambridgeshire, PE28 4HS England; Project ID No. ISK0315; 8/27/08); The skin of 3 New Zealand White rabbits was exposed to 0.5 g/site, one site/animal, of IKF-309 Technical (lot no. 0701; purity: 97.88%) for 4 hours under a semi-occlusive wrap. The treatment site was moistened with 0.5 ml of reverse osmosis water prior to the placement of the test material on the skin. No erythema nor edema was evident throughout the 72-hour observation period. Toxicity Category not assigned; Study unacceptable, possibly upgradeable with the assurance that the test material was adequately moistened while in contact with the skin. (Moore, 9/12/14)

Dermal sensitization

53251-0013; 278796; “IKF-309 Technical: Skin Sensitisation Study in Mice-Local Lymph Node Assay-(Final Revised Report)”; (T. Kosaka; The Institute of Environmental Toxicology, Joso-shi, Ibaraki 303-0043, Japan; Document ID No. IET 07-0113; 6/4/09, revised, 2/23/11); The dorsal skin on the ears of 5 female CBA/JNCrlj mice/group was treated by topical application with 25 ul/ear/day of 0 (vehicle: acetone/olive oil solution (4:1, v/v)) or 10, 25, or 50% preparations of IKF-309 Technical (lot no. 0701, purity: 97.88%) in the vehicle for 3 days. Three days later, 20 µCi of ³H-thymidine was injected iv into the tail vein of each animal and 5 hours later each animal was euthanized, ³H-thymidine incorporation and lymph node weights were used to assess the potential of the test material to elicit a sensitizing response. There was no indication of a dose-related proliferative response in any of the treatment groups. The positive control was functional. Study acceptable. (Moore, 9/15/14)

SUBCHRONIC STUDIES

Rat Subchronic Dietary Toxicity Study

** 53251-0015; 278799; “IKF-309 Technical: Repeated Dose 90-DayToxicity Study in Rats”; (R. Ohtsuka; The Institute of Environmental Toxicology, Joso-shi, Ibaraki, 303-0043 Japan; Project ID No. IET 06-0015; 1/19/10); Ten Fischer F344 rats/sex/group received 0, 300, 1000, 2500 or 5000 ppm of IKF-309 Technical (lot no. 0602; purity: 98.04%) in the diet for 13 weeks ((M) 0, 17.9, 60.5, 150, 305 mg/kg/day, (F) 0, 20.6, 69.0, 171, 350 mg/kg/day). No deaths resulted from the treatment. There were no apparent treatment-related clinical signs or effects noted in the functional observational battery or motor activity evaluation. There was no treatment-related effect upon the mean body weights or food consumption. In the ophthalmological examination and urinalysis, no treatment-related effects were noted. In the hematological evaluation, although there were some parameters for which the values for the 5000 ppm group were statistically different from that of the control group, no treatment-related effect was evident. In the clinical chemistry evaluation, the mean albumin and total protein levels were greater for the males in the 2500 and 5000 ppm groups (p<0.01). The globulin levels were elevated for the 5000 ppm males as well (p<0.01). The total protein and globulin levels in the serum of the 5000
ppm females were elevated in comparison to the control (p<0.05 or 0.01). The BUN level for the 5000 ppm males was greater than that of the control group (p<0.01). Serum total bilirubin was reduced for both sexes in the 2500 and 5000 ppm groups (p<0.01). The mean relative liver weights for both sexes in the 2500 and 5000 ppm groups and for the 1000 ppm males were greater than those values for the control (p<0.01). The mean relative kidney weights for both sexes in the 5000 ppm group and the 2500 ppm males were greater than those values for the control (p<0.01 or 0.05). The mean relative cecum weights of both sexes in the 5000 ppm and the females in the 2500 ppm group were greater than those values for the control (p<0.01). In the histopathology examination, diffuse hepatocellular hypertrophy was noted in the livers of both sexes in the 5000 ppm group ((M), 0: 0/10 vs. 5000: 9/10; (F), 0: 0/10 vs. 5000: 6/10). Deposition of hyaline droplets in the proximal tubules of the kidney was noted for the males of the 5000 ppm group (0: 0/10 vs. 5000: 9/10). In addition, tubular basophilic change in the kidney was evident for the 2500 and 5000 ppm males (0: 0/10 vs. 2500: 4/10, 5000: 7/10). No adverse effects were evident. Target organs: liver and kidney. Rat Subchronic Dietary NOEL: 1000 ppm ((M) 60.5 mg/kg/day, (F) 69.0 mg/kg/day) (based upon increased relative liver and/or kidney weights for both sexes in the 2500 ppm treatment group); Study acceptable. (Moore, 9/22/14)

**Dog Subchronic Dietary Toxicity Study**

53251-0016; 278801; “IKF-309 Technical: Repeated Dose 90-DayToxicity Study in Dogs”; (N. Nakashima; The Institute of Environmental Toxicology, Joso-shi, Ibaraki, 303-0043 Japan; Project ID No. IET 06-0109; 1/15/10); Four beagle dogs/sex/group were dosed with 0, 500, 3000, 15000 (females only) or 25000 (males only) ppm of IKF-309 Technical (lot no. 0701; purity: 97.88%) for 13 weeks ((M): 0, 15.0, 90.3 and 776 mg/kg/day, (F) 0, 15.3, 89.8. and 475 mg/kg/day, respectively). No mortality resulted from the treatment. There was no treatment-related effect upon the mean body weights or food consumption. One female in the 3000 ppm group and two females in the 25000 ppm group exhibited corneal opacity after 13 weeks of treatment. In the urinalysis, one male in the 3000 ppm and two males in the 25000 ppm group demonstrated the presence of bilirubin (+) in the urine after 13 weeks of treatment. There was no treatment-related effect upon the hematological parameters. In the clinical chemistry evaluation, serum alkaline phosphatase activity was elevated for the males in the 25000 ppm and for the females in the 15000 ppm groups after 7 and 13 weeks of treatment (NS, p<0.01). The serum triglyceride level of the males in the 25000 ppm group was increased after 7 and 13 weeks of treatment (p<0.05 or 0.01). The mean absolute and relative liver weights were greater for the both sexes in the high dose groups (p<0.05 or 0.01, NS). The histopathological examination revealed the presence of centrilobular hepatocellular hypertrophy in the livers of both sexes in the high dose groups. **No adverse effect indicated. Dog Subchronic Dietary NOEL:** (M/F) 3000 ppm (M) 90.3 mg/kg/day, (F) 89.8 mg/kg/day) (based upon the treatment-related effects on the liver of the males in the 2500 ppm group and the females in the 15000 ppm group); **Study acceptable.** (Moore, 9/24/14)

**Rat 28-Day Repeated Dosing Dermal Toxicity Study**

53251-0017; 278803; “IKF-309: Toxicity Study by Dermal Administration to CD Rats for 4 Weeks”; (S. Cooper; Huntingdon Life Sciences Ltd, Alconbury, Huntingdon, Cambridgeshire, PE28 4HS England; Project ID No. JSM0033; 3/15/10); The skin of 10 Cr:CD (SD) rats/sex/group was treated with 0, 100, 300 or 1000 mg/kg/day of IKF-309 Technical (lot no. 0701; purity: 97.88%) for 6 hours/day for 4 weeks. The test material was not directly moistened. Purified water was placed on the application site and on the gauze overlying the material. No mortality resulted from the treatment. The mean body weights and food consumption were not affected by the treatment. The prothrombin and activated partial thromboplastin times (APTT) were increased for the females in the 1000 mg/kg group over that of the control group (p<0.05
or 0.01). However, the values were within the historical control range. There were no treatment-related effects on either clinical chemical parameters or urinalysis. The mean organ weights were not affected by the treatment. There were no treatment-related lesions in the histological examinations. **No adverse effect indicated.** Reported Rat Repeated Dosing 4-Week Dermal Toxicity NOEL: (Systemic) (M/F) 1000 mg/kg/day (based upon the lack of toxicologically significant treatment-related effects upon both sexes in the 1000 mg/kg treatment group; (Dermal) (M/F) 1000 mg/kg/day (based upon the lack of treatment-related dermal effects in the 1000 mg/kg treatment group). **Study unacceptable**, possibly upgradeable to acceptable with information detailing the adequacy of the moistening procedure. (Moore, 9/25/14)

**Mouse Subchronic Dietary Toxicity Study**

53251-0014; 278797; “IKF-309: Toxicity Study by Dietary Administration to CD-1 Mice for 13 Weeks”; (E.L. Moore; Huntingdon Life Sciences Ltd., Alconbury, Huntingdon, Cambridgeshire, PE28 4HS England; Project ID No. ISK0291; 7/6/09); Ten Crl: CD1 (ICR) mice/sex/group received 0, 300, 1000, 3000 or 7000 ppm of IKF-309 Technical (lot no. 0701; purity: 97.88%) in the diet for 13 weeks ((M) 0, 53.2, 175.6, 514.7, 1318.1 mg/kg/day, (F) 0, 60.5, 213.9, 695.2, 1503.6 mg/kg/day). No deaths resulted from the treatment. There were no treatment-related effects upon the mean body weight gain or food consumption. In the hematological evaluation, the mean white blood cell count for the control group males was unusually low thereby the values for the treated groups were statistically greater. However, no treatment-related effect was apparent. In the clinical chemistry evaluation, although various parameters for the treated groups were statistically significant in relation to those of the control group, no treatment-related effect was noted. Although significantly increased adjusted liver weights were noted at 1000 (females only) or 3000 ppm (both sexes), only histological evidence of an effect was evident for both sexes in the 7000 ppm treatment group. Histopathological evaluation revealed hepatocytic hypertrophy in the livers of both sexes in the 7000 ppm group. **No adverse effect indicated.** Mouse Subchronic Dietary Toxicity NOEL: (M/F) 3000 ppm ((M) 514.7 mg/kg/day, (F) 695.2 mg/kg/day ) (based upon the increased adjusted liver weights and hepatocytic hypertrophy noted in the livers of both sexes in the 7000 ppm treatment group) **Study supplemental** (no ophthalmological examination was performed). (Moore, 9/16/14)

**CHRONIC STUDIES**

**Chronic, rat**

53251-0018; 278804; “IKF-309 Technical: Repeated Dose 1-Year Oral Toxicity Study in Rats”; (R. Ohtsuka; The Institute of Environmental Toxicology, Joso-shi, Ibaraki 303-0043, Japan; Project ID No. IET 06-0085; 1/19/10); Twenty Fischer F344 rats/sex/group received 0, 200, 1000 or 5000 ppm of IKF-309 Technical (lot no. 0701; purity: 97.88%) in the diet for 52 weeks ((M) 8.5, 42.9, 226 mg/kg/day, (F) 0, 10.6, 53.5, 275 mg/kg/day). One male in the 200 ppm group and one male in the 5000 ppm group died during weeks 46 and 40, respectively. No treatment-related clinical signs were evident in the detailed observations or the FOB/motor activity assessment. The mean body weights of the 5000 ppm females were lower than those of the control groups over the last 6 months of the study (p<0.01). There was no apparent treatment-related effect on the food consumption. The ophthalmological examination did not reveal any treatment-related ocular lesions. In the urinalysis, an increased ketone level was noted in the urine of the 5000 ppm females over the course of the study (p<0.01). In the hematological evaluation, the mean hematocrit, hemoglobin concentration and red blood cell counts of both sexes in the 5000 ppm group were reduced in comparison the control values over the course of the study (p<0.01 or 0.05). However, the effects were not toxicologically significant. The prothrombin and activated partial thromboplastin (APTT) times for the 5000 ppm males and the APTT value for the 5000 ppm females were increased after 52 weeks of
In the clinical chemistry evaluation, the mean serum alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase activity levels were reduced for both sexes in the 5000 ppm group over the course of the study (p<0.01 or 0.05). Serum creatinine was reduced for both sexes in the 5000 ppm group throughout the study (p<0.01). The total protein, albumin and globulin levels were elevated in the serum for both sexes in the 5000 ppm group through 26 weeks and for the 5000 ppm females after 52 weeks. The blood urea nitrogen was increased in the serum of the 5000 ppm males through 26 weeks of treatment (p<0.01). The serum cholesterol levels were greater for both sexes in the 5000 ppm group through 26 weeks of treatment and for the 5000 ppm females through 52 weeks (p<0.01). The serum triglyceride and total bilirubin levels were lower for both sexes in the 5000 ppm group throughout the study (NS, p<0.01 or 0.05). The serum calcium concentrations were elevated for both sexes in the 5000 ppm group after 26 weeks of treatment and for the 5000 ppm females through 52 weeks (p<0.01). In contrast, the serum chloride levels were reduced for both sexes in the 5000 ppm group through 26 weeks and for the 5000 ppm females through 52 weeks (p<0.01 or 0.05). In the necropsy examination, distention of the large intestine was noted for 5 males and 10 females in the 5000 ppm group. The mean absolute and relative liver, kidney and cecum weights for both sexes in the 5000 ppm group were greater than those values for the control (p<0.01). In the histopathology examination, centrilobular hepatocellular hypertrophy was noted in the livers of the 5000 ppm males ((M), 0: 0/20 vs. 5000: 18/20). Tubular basophilic change was noted in the kidneys of the 5000 ppm males (0: 1/20 vs. 5000: 10/20). Increased deposition of brown pigment in the tubular cells of the kidneys of the 5000 ppm females was noted (0: 0/20 vs. 5000: 20/20). No adverse effects were evident. Target organs: liver and kidney. Rat Chronic Dietary NOEL: (M/F) 1000 ppm ((M) 42.9 mg/kg/day, (F) 53.5 mg/kg/day) (based upon the treatment-related effects on various parameters in clinical chemistry and the necropsy/histological lesions noted for both sexes in the 5000 ppm group). Study acceptable. (Moore, 9/30/14)

Chronic, dog
** 53251-0019; 278806; “IKF-309 Technical: Repeated Dose 1-Year Oral Toxicity Study in Dogs”; (N. Nakashima; The Institute of Environmental Toxicology, Joso-shi, Ibaraki 303-0043, Japan; Project ID No. IET 06-0110; 1/15/10); Four beagle dogs/sex/group were dosed with 0, 500, 3000, 15000 (females only) or 25000 (males only) ppm of IKF-309 Technical (lot no. 0701; purity: 97.88%) for 52 weeks ((M): 0, 13.7, 83.5 and 701 mg/kg/day, (F) 0, 14.1, 86.2. and 448 mg/kg/day, respectively). No mortality resulted from the treatment. The mean body weight gain of the males in the 25000 ppm group was less than that of the control group over the course of the study. The mean food consumption for this group was also less than that of the control group. No treatment-related effect was noted in the ophthalmological examination. Except for a lower range of pH values for the urine of the males in the 25000 ppm group at 26 and 52 weeks of treatment (p<0.05), there were no other treatment-related effects noted in the urinalysis. In the hematology examination, although various parameters were statistically different between the treated animals and the control group, no toxicologically significant effects were evident. In the clinical chemistry evaluation, serum alkaline phosphatase activity was elevated for the males in the 25000 ppm and for the females in the 15000 ppm groups throughout the study (p<0.01 or 0.05). The serum gamma glutamyl transpeptidase activity was elevated for the males in the 25000 ppm group. The mean absolute and relative liver weights were greater for both sexes in the high dose groups (NS, p<0.01 or 0.05). The histopathological examination revealed the presence of centrilobular hepatocellular hypertrophy in the livers of the 25000 ppm males. No adverse effect indicated. Dog Chronic Dietary Toxicity NOEL: (M/F) 3000 ppm ((M) 83.5 mg/kg/day, (F) 86.2 mg/kg/day) (based upon the increased serum alkaline
phosphatase activity and effects on the liver noted for both sexes in the highest treatment groups); Study acceptable. (Moore, 10/1/14)

**Oncogenicity, rat**

** 53251-0021; 278809; “IKF-309 Technical: Carcinogenicity Study in Rats”; (R. Ohtsuka; The Institute of Environmental Toxicology, Joso-shi, Ibaraki, 303-0043 Japan; Project ID No. IET 06-0086; 1/19/10); Fifty two Fischer F344 rats/sex/group received 0, 200, 1000 or 5000 ppm of IKF-309 Technical (lot no. 0701; purity: 97.88%) in the diet for 104 weeks ((M) 0, 7.25, 36.4, 197 mg/kg/day, (F) 0, 9.13, 46.5, 254 mg/kg/day). Mortality of the 5000 ppm males was increased over that of the control group by the conclusion of the study. Except for an increased incidence of soiled fur for both sexes in the 5000 ppm treatment group (p<0.01), no treatment-related effects were noted in the clinical observations. The mean body weights of both sexes in the 5000 ppm group were less than those of the control group over much of the study period (p<0.01). However, the mean food consumption of these animals was greater than that of the control group throughout the study. The hematology evaluation did not reveal any treatment-related effect on the total or differential white blood cell counts. In the necropsy examination, distention of the large intestine was noted for both sexes in the 5000 ppm group (p<0.01). The mean relative liver, kidney, cecum and heart weights for both sexes in the 5000 ppm group were greater than the control group values (p<0.01). In the histopathological examination, dilation of the mesenteric lymph node sinus was noted for the 5000 ppm males (p<0.01). In the liver of both sexes in the 5000 ppm group, increased incidences of fatty changes and hypertrophy were noted for the centrilobular hepatocytes (p<0.01 or 0.05). Necrosis of centrilobular hepatocytes was evident in the livers of the 5000 ppm males (p<0.01). Focal congestion was noted in the livers of the 5000 ppm females (p<0.01). An increased incidence of chronic nephropathy was evident in the kidneys of the 1000 and 5000 ppm females (p<0.01). No increase in the incidence of tumors, benign or malignant, was noted for either sex. Possible adverse effect (non-neoplastic): hepatocytic necrosis; Rat Chronic Dietary NOEL: (M) 1000 ppm (36.4 mg/kg/day) (based upon the treatment-related effects noted on the liver of the males in the 5000 ppm treatment group) (F) 200 ppm (9.13 mg/kg/day) (based upon the increased incidence of chronic nephropathy in the kidneys of the 1000 ppm females); Oncogenicity was not evident. Study acceptable. (Moore, 10/3/14)

**Oncogenicity, mouse**

** 53251-0020; 278807, 278808; “IKF-309: Carcinogenicity Study by Dietary Administration to CD-1 Mice for 78 Weeks”; (E.L. Moore; Huntingdon Life Sciences Ltd., Alconbury, Huntingdon, Cambridgeshire, PE28 4HS England; Project ID No. ISK0305; 1/26/10); Fifty two male Crl: CD1 (ICR) mice/group received 0, 600, 1800 or 5400 ppm of IKF-309 Technical (lot no. 0701; purity: 97.88%) in the diet for 78 weeks. Fifty two female Crl: CD1 (ICR) mice/group received 0, 300, 1000 or 3000 ppm of the test material in the diet for the same time period ((M) 0, 77.6, 237.2, 716.2 mg/kg/day, (F) 0, 49.4, 166.8, 486.0 mg/kg/day). No treatment-related increase in mortality was evident. The mean body weight gain and food consumption of the 3000 ppm females was less than that of the control group over the course of the study. Detailed clinical observations did not reveal any apparent treatment-related signs except for the greater incidence of peritoneal staining in the 5400 ppm males. No treatment-related effect was evident on the differential white blood cell count in the blood smears. An increased incidence of combined hepatocellular adenoma and hepatocellular carcinoma was noted in the livers of the treated males (0: 4/52, 600: 9/52, 1800: 9/52, 5400: 12/52). An increased incidence of hepatocellular hypertrophy was evident in the livers of the males in the 600 ppm treatment group and above (p<0.01). An increased incidence of individual hepatocyte necrosis was evident in the livers of males in the 1800 and 5400 ppm treatment groups (p<0.05). The kidneys of the males in the 5400 ppm group demonstrated an increased incidence of cortical
scarring (p<0.05). An increased incidence of cortical tubular basophilia was evident in the kidneys of the 1800 and 5400 ppm males (p<0.05). Acinar hyperplasia was noted in the prostates of the 5400 ppm males (p<0.05). Histopathological lesions for the females were limited to the 3000 ppm treatment group. Their livers demonstrated an increased incidence of pigment in macrophages and increased incidences in chronic progressive nephropathy in the kidneys and involution/atrophy in the thymus were noted as for this group. Possible adverse effect: increased incidence of hepatocellular oncogenicity. Mouse Chronic Dietary Toxicity NOEL: (M) < 600 ppm (<77.6 mg/kg/day) (based upon the increased incidence of hepatocellular hypertrophy in the liver of the 600 ppm males); (F) 1000 ppm (166.8 mg/kg/day) (based upon the increased incidence of chronic progressive nephropathy in the kidneys and involution/atrophy in the thymus of the 3000 ppm females); Increased incidence of hepatocellular oncogenicity. Study acceptable. (Moore, 10/2/14)

GENOTOXICITY

Gene mutation
** 53251-0026; 278816; “IKF-309 Technical: Bacterial Reverse Mutation Test”; (K. May; Huntingdon Life Sciences Ltd., Alconbury, Huntingdon, Cambridgeshire, PE28 4HS, England; Report No. IDK 0311/073744; 10/17/07); In the 1st trial, *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 and *E. coli* WP2uvrA were exposed to IKF-309 Technical (lot no. 0701, purity: 97.88%) at concentrations ranging from 5 to 5000 µg/plate for 72 hours at 37°C, using the plate incorporation technique. In the 2nd trial, the same strains were exposed to the same concentrations of the test material for 30 minutes at 37°C during a pre-incubation period followed by exposure for 72 hours at 37°C. Both trials were performed under conditions of non-activation and activation. There were 3 plates per treatment level. An S9 fraction derived from the liver of rats pretreated with phenobarbital/5,6-benzoflavone was used to metabolize the test material. Precipitation of the test material was noted in the 1500 and 5000 µg/plate treatments for all of the assays. There was no treatment-related increase in the incidence of reverse mutation. No adverse effect indicated. The positive controls were functional. Study acceptable. (Moore, 10/16/14)

** 53251-0026; 278817; “IKF-309 Technical: In Vitro Mutation Test Using Mouse Lymphoma L5178Y Cells”; (L. Hynes; Huntingdon Life Sciences, Eye Research Centre, Eye, Suffolk, IP23 7PX, UK; Report No. ISK/0310; 9/19/08); Mouse lymphoma L5178Y cells (clone 3.7.2 (TK +/- )) were treated with IKF-309 Technical (lot no. 0701, purity: 97.88%) at concentrations ranging from 9.93 to 1271 µg/ml for 3 hours under conditions of non-activation and activation and at concentrations ranging from 5 to 125 µg/ml for 24 hours under conditions of non-activation at 37°C. One trial was performed with duplicate cultures/treatment level. A phenobarbital/5,6-benzoflavone-induced rat liver S9 fraction was used to metabolize the test material. Cell survival and mutation frequency for each treatment level were determined and compared to those of the solvent control. There was no increase in the mutation frequency under either conditions of non-activation or activation. No adverse effect indicated. Positive controls were functional. Study acceptable. (Moore, 10/17/14)

Chromosome damage
** 53251-0026; 278818; “IKF-309 Technical: In Vitro Mutation Mammalian Chromosome Aberration Test in CHL Cells”; (L. Pritchard; Huntingdon Life Sciences, Alconbury, Huntingdon, Cambridgeshire, PE28 4HS, England; Report No. ISK/0322; 2/14/08); Cultures of Chinese Hamster lung (CHL) cells were treated with concentrations of IKF-309 Technical (lot no. 0701, purity: 97.88%) ranging from 30 to 90 µg/ml under conditions of non-activation for 3 hours followed by a recovery period of 12 hours of incubation in the 1st trial and ranging from 2.5 to 70
µg/ml for 15 hours in the 2nd trial. Under conditions of activation, the cells were exposed to concentrations of the test material ranging from 70 to 200 µg/ml in the 1st trial and ranging from 70 to 150 µg/ml in the 2nd trial. Both treatments were for 3 hours followed by an additional 12 hours of incubation. A phenobarbital/5,6-benzoflavone-induced rat liver S9 fraction was used to metabolize the test material. One hundred metaphases/replicate were examined for structural abnormalities. A statistically significant increase in chromosomal aberrations was evident under conditions of non-activation at 70 µg/ml in the 1st trial (p<0.01). However, this effect was not evident in the 2nd trial. No adverse effect was evident. The positive controls were functional. Study acceptable. (Moore, 10/20/14)

DNA damage or miscellaneous effects
** 53251-0026; 278819; “IKF-309 Technical: Mouse Micronucleus Test”; (G. Hynes; Huntingdon Life Sciences, Eye Research Centre, Eye, Suffolk, IP23 7PX, UK; Report No. ISK/0327; 4/29/08); Five CD1 mice/sex/group were dosed orally by gavage with 0 (vehicle: 1% CMC), 500, 1000 or 2000 mg/kg of IKF-309 Technical (lot no. 0701, purity: 97.88%). An additional 5 animals/sex/group were dosed with 0 or 2000 mg/kg of the test material. Five animals/sex were also dosed orally with 12 mg/kg of Mitomycin C. Five animals/sex/group were euthanized at 24 hours post-dose (note: this included the 5 animals/sex in the positive control group as well). The remaining 5 animals/sex/group in the control and 2000 mg/kg groups were euthanized at 48-hours post-dose. The number of micronucleated polychromatic (PCE)/2000 PCEs and the percentage of PCEs to the total erythrocyte population were reported. There was no treatment-related increase in the percentage of micronucleated PCEs. No adverse effect indicated. The positive control was functional. Study acceptable. (Moore, 10/20/14)

REPRODUCTIVE TOXICITY, RAT
** 53251-0025; 278815; “IKF-309 Technical: A Reproduction Toxicity Study in Rats”; (H. Hojo; The Institute of Environmental Toxicology, Joso-shi, Ibaraki, 303-0043 Japan: Project ID No. IET 06-0112; 10/13/09); In a two-generation reproduction study, 24 Wistar Hannover rats/sex/group in the P generation received 0, 150, 1000, or 5000 ppm of IKF-309 Technical (lot no. 0701, purity: 97.88%) in the diet for 10 weeks prior to mating, during mating, and during the 3 weeks each of gestation and lactation. At that time, 24 F1 animals/sex/group were selected as parents and treated with the same dosing regimens for 10 weeks, followed by mating and 3 weeks each for gestation and lactation of the F2 generation ([(M) P: 0, 11.9, 79.2, 395 mg/kg/day; gestation and lactation: 0, 16.7, 105.6, 370 mg/kg/day, F1: premating: 0, 13.0, 484.4, 434 mg/kg/day; gestation and lactation: 0, 13.8, 90.7, 453 mg/kg/day, Overall average, P: 0, 13.8, 90.7, 453 mg/kg/day, F1: 0, 14.4, 92.3, 485 mg/kg/day]. One male and one female in the 1000 ppm group of the P generation died on study weeks 11 and 2, respectively. There was no treatment-related effect upon the mean body weight gains and food consumption of both parental generations. In the hematology evaluation, the mean hematocrit percentage, hemoglobin concentrations and red blood cell counts for both sexes in the 5000 ppm of both parental generations were less than the control values (NS, p<0.01 or 0.05). The mean absolute and/or relative liver, kidney, thyroid, and cecum weights of both sexes in the 5000 ppm group of both generations were greater than the values of the control group (NS, p<0.01 or 0.05). In the histopathological examination, hepatocytic hypertrophy was noted in the livers of both sexes in the 5000 ppm group of both generations (p<0.01). Deposition of brown pigment in the liver was also noted for the 5000 ppm males in both generations. Increased deposition of hyaline droplets in the renal proximal tubules was exhibited in 5000 ppm males of both generations (p<0.01). An increased incidence of follicular cell hypertrophy in the thyroid glands was noted for the 5000 ppm females of both generations and for the 5000 ppm males in the F1
generation (p<0.01). No treatment-related lesions were evident in the reproductive tissues and organs of either generation. No treatment-related effect upon time to vaginal opening or preputial separation was evident for the F1 generation. There was no treatment-related effect upon gestational time. The fertility and gestation indices were not affected. The mean litter sizes of the treated groups were similar to those of the control. In the developmental phase of the study, the mean body weights of the 5000 ppm offspring in both generations were less than those of the control during the lactation period (NS, p<0.05). The mean absolute and/or relative spleen weights of the weanlings of both sexes in both generations of the 5000 ppm group were less than the control values (NS, p<0.01).  No adverse effect was evident. Parental NOEL: (M/F) 1000 ppm ((M) 76.8 mg/kg/day, (F) 92.3 mg/kg/day) (based upon histological lesions noted in the liver, kidneys and/or thyroid gland of both sexes in the 5000 ppm group); Reproduction NOEL: 5000 ppm (485 mg/kg/day) (based upon the lack of any treatment-related effects on the reproductive indices of the 5000 ppm group); Developmental NOEL: 1000 ppm (92.3 mg/kg/day) (based upon lower mean body weights for the pups of both generations in the 5000 ppm group); Study acceptable. (Moore, 10/10/14)
Twenty four mated female Wistar Hannover rats/group were dosed orally by gavage with 0 (vehicle: aqueous 1% sodium carboxymethyl cellulose), 30, 300 or 1000 mg/kg of IKF-309 Technical (lot no. 0701; purity: 97.88%) from day 6 through day 19 of gestation. No maternal deaths resulted from the treatment. The mean body weight gain of the dams in the 1000 mg/kg group was less than that of the control group between days 6 and 9 of gestation (NS). The mean food consumption of these dams was less than that of the control group values between gestation days 6 and 12 (p< 0.01). The mean absolute and relative liver weights of the 300 and 1000 mg/kg dams were greater than the control values (p<0.05 or 0.01). The mean absolute cecum weights of the 300 and 1000 mg/kg dams and the mean relative cecum weight of the 1000 mg/kg dams were greater than the values for the control group (p<0.05 or 0.01). The mean fetal weights of the male and female offspring of the 1000 mg/kg group were less than the control values (NS). There was no treatment-related increase in malformations. An increase in the incidence of discontinuous rib cartilage on a per litter basis was noted for the litters in the 1000 mg/kg group. No adverse effect indicated. Maternal NOEL: 30 mg/kg/day (based upon the increased absolute and relative liver weights of the 300 mg/kg females); Developmental NOEL: 300 mg/kg/day (based upon the increased litter incidence of fetuses having discontinuous rib cartilage); Study acceptable. (Moore, 10/7/14)

No adverse effects indicated. Study supplemental. (Moore, 10/6/14)

Rabbit

No adverse effects were indicated. Maternal NOEL: 100 mg/kg/day (based upon apparent effect on food consumption of the 300 mg/kg does and the incidence of two abortions for this group); Developmental NOEL: 300 mg/kg/day (based upon the lack of treatment-related effect on the does in the 300 mg/kg group); Study acceptable. (Moore, 10/8/14)
carboxymethyl cellulose), 30, 100, 300, or 1000 mg/kg/day of IKF-309 Technical (lot no. 0701; purity: 97.88%) from gestation day 6 through gestation day 27. No maternal deaths occurred during the study. The mean body weight gain and food consumption of the does in the 300 and 1000 mg/kg treatment groups were less than the control values. The mean relative liver weight of the does in the 1000 mg/kg group was greater than that of the control group (p<0.01). One doe in the 100 mg/kg group and 2 does in the 300 mg/kg group suffered total resorption of their embryos. Four of the does in the 1000 mg/kg group aborted or delivered prematurely. The mean body weights of the fetuses in the 300 and 1000 mg/kg groups were less than the control values. No treatment-related external malformations were evident. No adverse effect was evident. Study supplemental. (Moore, 10/7/14)

NEUROTOXICITY

**Rat Acute Neurotoxicity**
53251-0028; 278821; “IKF-309: Neurotoxicity Study by Single Oral Gavage Administration to CD Rats Followed by a 14 Day Observation Period”; (L.A.J. Powell; Huntingdon Life Sciences Ltd., Alconbury, Huntingdon, PE28 4HS, England; Report No. ISK0407; 1/12/10); Ten Crl:CD (SD) rats/sex/group were dosed orally by gavage with 0 (vehicle: aqueous 1% sodium carboxymethylcellulose), 125, 500 or 2000 mg/kg of IKF-309 Technical (batch no. 0701; purity: 97.88%). Functional Observational battery and motor activity evaluations were performed prior to dosing and at 4 hours post-dose and on days 8 and 15. Five animals/sex/dose were perfused whole body and pertinent nervous tissues were examined histologically. No deaths resulted from the treatment. There was no treatment-related effect upon the mean body weights. There were some apparent treatment-related effects on the animals at 4 hours post-dose. However, these results could not be attributed to a particular neurotoxic etiology. There were no treatment-related lesions noted in the histological evaluation of the nervous tissue. No adverse effect indicated. Rat Acute Oral Neurotoxicity NOEL: (M/F) > 2000 mg/kg; Study acceptable (Moore, 10/22/14)

**Rat Acute Neurotoxicity Dose Range-Finding**
53251-0027; 278820; “IKF-309 Technical: Dose Range and Time to Peak Effect in Rats by Acute Oral Administration”; (L.A.J. Powell; Huntingdon Life Sciences Ltd., Alconbury, Huntingdon, PE28 4HS, England; Report No. ISK0408; 11/5/09); Three Crl:CD(SD) rats/sex/group were dosed orally by gavage with 0 (vehicle: aqueous 1% sodium carboxymethylcellulose), 500 or 2000 mg/kg of IKF-309 Technical (lot no. 0701; purity: 97.88%). Functional observational batteries (FOB) were performed on each group of animals prior to dosing and at 2, 3, 4 and 6 hours post-dose. No deaths resulted from the treatment. No specific clinical signs related to the treatment were identifiable in the FOB evaluations. No time to peak effect could be ascertained. Study supplemental. (Moore, 10/21/14)

**Rat Subchronic Neurotoxicity Study**
** 53251-0029; 278822; “IKF-309: Neurotoxicity Study by Dietary Administration to CD Rats for 13 Weeks”; (W. Arrowsmith; Huntingdon Life Sciences Ltd., Alconbury, Huntingdon, PE28 4HS, England; Project ID No. JSM0027; 3/16/10); Ten Crl: CD (SD)IGS BR rats/sex/group received 0, 1000, 5000, or 15000 ppm of IKF-309 Technical (batch no. 0701; purity: 97.88%) in the diet for 13 weeks (M) 0, 62, 310, 927 mg/kg/day, (F) 0, 77, 378, 1147 mg/kg/day). The mean body weight gains of both sexes in the 15000 ppm group and the males in the 5000 ppm group were less than those of the control group over the course of the study (NS, p<0.05). There was no apparent treatment-related effect on food consumption. There were no apparent treatment-related effects noted in the FOB and motor activity assessments over the course of the study. Brain morphometry did not reveal any treatment-related effect. Histopathological examination
of the nerve tissues did not reveal any treatment-related lesions. **No adverse effect indicated.**

**Rat Subchronic Neurotoxicity NOEL:** (M/F) > 15000 ppm ((M) 927 mg/kg/day, (F) 1147 mg/kg/day) (based upon the lack of neurotoxic effects in the 15000 ppm treatment group). **Study acceptable.** (Moore, 10/23/14)

**Developmental neurotoxicity, rat**

Not required at this time.

**Delayed neurotoxicity, hen**

Not required at this time.

**IMMUNOTOXICITY**

**Mouse 28-Day Dietary Immunotoxicity**

** 53251-0034; 278827; “IKF-309: 4-Week Dietary Immunotoxicity Study in the Female Mouse”; (M-C. Laurent; Huntingdon Life Sciences Ltd., Alconbury, Huntingdon, PE28 4HS, England; Project ID No. JSM0036; 3/1/10); Ten female CD1 mice/group received 0, 1000, 3000 or 7000 ppm of IKF-309 Technical (lot no. 0701; purity: 97.88%) in the diet for 4 weeks (0, 192, 553, 1270 mg/kg/day). Another 8 females were dosed orally by gavage with 20 mg/kg/day of cyclophosphamide on study days 22 through 26 as the positive control group. On day 25, five days before necropsy on day 29, each animal received an iv injection of 4x10^8 sheep red blood cells (SRBC). SRBC specific IgM plaques were determined for each animal by incubating a spleen cell suspension preparation with guinea pig complement and SRBC. No deaths occurred during the treatment period. The mean body weights and food consumption were not affected by the treatment. There were no treatment-related lesions noted in the necropsy examination. There was no treatment-related effect on the spleen or thymus weights. No treatment-related effect was evident in the plaque-forming cell assay. **No adverse effect indicated.** The positive control was functional. **Study acceptable.** (Moore, 11/5/14)

**Rat 28-Day Dietary Immunotoxicity**

** 53251-0035; 278828; “IKF-309: 4-Week Dietary Immunotoxicity Study in the Female Rat”; (P.R. Chambers; Huntingdon Life Sciences Ltd., Alconbury, Huntingdon, PE28 4HS, England; Project ID No. JSM0037; 3/1/10); Ten female Crl:CD(SD) rats/group received 0, 2000, 6000 or 20000 ppm of IKF-309 Technical (lot no. 0701; purity: 97.88) in the diet for 4 weeks (0, 179, 505, 1690 mg/kg/day). Another 8 females were dosed by intravenous injection with 50 mg/kg of cyclophosphamide on day 27 as the positive control group. On day 25, five days before necropsy on day 29, each animal received an iv injection of 2x10^8 sheep red blood cells (SRBC). SRBC specific IgM plaques were determined for each animal by incubating a spleen cell suspension preparation with guinea pig complement and SRBC. No deaths occurred during the treatment period. The mean body weight gain of the 20000 ppm animals was less than that of the control group (p<0.01). Food consumption of the 20000 ppm group was less than that of the control group throughout the study. There were no treatment-related lesions noted in the necropsy examination. No treatment-related effect on the spleen or thymus weights was noted in the necropsy. There was no treatment-related effect evident in the plaque-forming cell assay. **No adverse effect indicated.** The positive control was functional. **Study acceptable.** (Moore, 11/6/14)

**ENDOCRINE DISRUPTOR STUDIES**

Not submitted nor required at this time.
SUPPLEMENTAL STUDIES

None.