CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
HUMAN HEALTH ASSESSMENT BRANCH

SUMMARY OF TOXICOLOGY DATA
Isofetamid

Chemical Code # 6114, Document Processing Number (DPN) # 53207

11/5/13, 7/1/15

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, possible adverse effect
Oncogenicity, mouse:	No data gap, no adverse effect
Reproduction, rat:	No data gap, possible 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 required at this time

Toxicology one-liners are attached.

All record numbers through 284404 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
File name: T150701 prepared by H. Green

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

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METABOLISM AND PHARMACOKINETICS

**53207-0026 271157, "[^{14}C]IKF-5411: Absorption, Distribution, Metabolism and Excretion in the Rat," (T. Hardwick, Covance Laboratories Limited, Harrogate, North Yorkshire, UK., Covance Study Number 2244/080, November 28, 2011). Four to 18 Han Wistar (Crl: WI(Han)) rats per sex per group received a single dose or 14 consecutive daily doses of [^{14}C-Ph]IKF-5411 (benzene ring radiolabel) or [^{14}C-Th]IKF-5411 (thiophene ring radiolabel) at 5 or 200 mg/kg(day) by oral gavage. In excretion -balance investigations, recoveries of radiolabel were > 89% of administered dose. Excretion was rapid with the majority of radioactivity recovered within 48 hours post-dosing. Seventy-one to 73% (at 5 mg/kg) and 88% to 95% (at 200 mg/kg) for males and 37% to 38% (at 5 mg/kg) and 71% to 82% (at 200 mg/kg) for females was eliminated in feces, and urinary excretion of radiolabel accounted for 11% to 13% (at 5 mg/kg) and 3% to 8% (at 200 mg/kg) for males and 47% to 50% (at 5 mg/kg) and 11% to 23% (at 200 mg/kg) for females. Radiolabel in expired air was below the limit of quantification. The tissues and residual carcasses of males contained ~13-fold more radioactivity than females after a 5 mg/kg dose of the benzene ring radiolabel but only ~4 fold more after the thiophene ring radiolabel. Following the 200 mg/kg dose with both radiolabels, radioactivity levels in the tissues and residual carcasses of males and females were comparable. Repeated dosing had minimal effect on routes and rates of elimination. In blood and plasma pharmacokinetics investigations, maximum concentrations of radioactivity (C_{max}) were reached at ~4 to 6 (males) and ~2 (females) hours at 5 mg/kg and at ~6 to 8 (males) and ~8 (females) hours at 200 mg/kg. Plasma elimination half-lives ($T_{1/2}$) were ~38 hours regardless of sex, dose level, or radiolabel position. Exposure (area under the time/concentration curve (AUC)) was ~2-fold greater in males. Pharmacokinetics of IKF-5411 were not linear since the 40-fold increase from low dose to high produced only a ~25-fold increase in C_{max} and AUC indicating routes of absorption at the high dose were saturated. In bile-cannulated rats after a 5 mg/kg dose, minimal differences were noted in the rates and routes of excretion between the 2 radiolabels. Eighty-eight % (males) and 83% to 85% (females) of radioactivity was excreted in bile, 7% to 8% (males) and 8% to 9% (females) in feces, and 6% to 8% (males) and 10% to 15% (females) in urine. Absorption of IKF-5411, calculated from radioactivity recovered in bile, urine, and carcass was > 93% of dose. In tissue distribution investigations, there were no sex differences nor radiolabel position effects on tissue distribution of radioactivity, and there was no evidence of accumulation of radioactivity in tissues following repeated dosing. The liver was the predominate tissue from which radiolabel was recovered. Radioactivity was rapidly and widely distributed throughout the tissues and organs by 4 hours (low dose)/8 hours (high dose) after a single dose of radiolabel. By 40 hours for the low dose or 48 hours for the high dose, radioactive concentrations had declined by between 2 and 55-fold from the first sampling times and, at the terminal sampling, by ~600-fold. IKF-5411 underwent extensive metabolism after oral administration. There were quantitative, but not qualitative, differences in metabolism due to the position of the radiolabel in the metabolism of IKF-5411 along with a quantitative sex difference related to differences in

excretion patterns between males and females. After oral dosing of rats with either [^{14}C-Ph]IKF-5411 or [^{14}C-Th]IKF-5411, metabolites in urine included M3 (4HP glucuronide), PPA, and 4HP. None of the metabolites in urine were produced by cleavage of the benzene or thiophene-ring structures, and there was minimal difference in the components of urine between the 2 radiolabeled forms. Common metabolites in feces after dosing with either radiolabel were M8 (5-HPPA), PPA, M9 (hydroxy methylated PPA), M10 (hydroxy 4HP), M11(hydroxy IKF-5411), and 4HP. Additionally, the presence of M6 (hydroxy IBA) was noted following administration of [^{14}C-Ph]IKF-5411 (produced by cleavage between the benzene and thiophene-ring structures). IKF-5411 was also present in the feces possibly due to unabsorbed dose. In biliary cannulated rats, the urinary metabolites were the same as in non-cannulated rats. Metabolites in bile included MI (O-sulphate IKF-5411), M2 (O-dealkylated, hydroxylated, glucuronidated IKF-5411), M3 (4HP glucuronide), M4 (4-HPPA), PPA, M5 (hydroxylated, glucuronidated IKF-5411), and 4HP. IKF-5411 was a minor component of bile. None of the metabolites in bile resulted from cleavage between the benzene and thiophene-ring structures. The proposed metabolic pathway includes 3 main routes: O-deakylation, hydroxylation, and subsequent glucuronidations. Minor routes include methylation, sulphation, and cleavage between the benzene and thiophene ring structures. A schematic of the proposed metabolic pathway is included. Acceptable. (Green, 10/24/13).

GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT

Acute oral toxicity

**53207-0008 271128, "IKF-5411 Technical: Acute Oral Toxicity to the Rat (Acute Toxic Class Method)," (E. L. Moore, Huntingdon Life Sciences Ltd., Alconbury, Huntingdon, Cambridgeshire, England, Laboratory Project No. JSM0141, December 20, 2010). Two groups of 3 female CD (Crl:CD 'SD') rats received a single oral gavage dose of IKF-5411 Technical (96.68% isofetamid) at 2000 mg/kg (the second group was dosed 2 days after the first group) followed by a 14-day observation period. Animals were fasted overnight before dosing and access to food was reinstated 4 hours post-dosing. No clinical signs of reaction to treatment were indicated during the study. All animals survived through the 14-day observation period and gained bodyweight. Necropsy results were unremarkable. $LD_{50} \geq 2000$ mg/kg. Toxicity category III. Acceptable. (Green, 8/8/13).

Acute dermal toxicity

**53207-0008 271129, "IKF-5411 Technical: Acute Dermal Toxicity to the Rat," (E. L. Moore, Huntingdon Life Sciences Ltd., Alconbury, Huntingdon, Cambridgeshire, England, Laboratory Project No. JSM0142, December 20, 2010). Five CD (Crl:CD 'SD') rats per sex received a single 24 hour dermal exposure (clipped, unabraded, occluded skin) to IKF-5411 Technical (96.68% isofetamid) at 2000 mg/kg followed by a 14 day observation period. All animals survived to the end of the observation period and no treatment-related clinical signs or necropsy findings were indicated. No dermal reactions were observed during the study. All animals gained bodyweight during the study. LD_{50} (males and females) > 2000 mg/kg. Toxicity category III. Acceptable. (Green, 8/9/13).

Acute inhalation toxicity

**53207-0008 271130, "IKF-5411 TGAI: Acute 4 Hour (Nose Only) Inhalation Study in the Rat," (V. Leighton, Covance Laboratories, Harrogate, North Yorkshire, England, Covance study No. 8224246, November 2, 2010). Three HsdHan™: WIST rats per sex were exposed to IKF-5411 Technical (96.68% w/w isofetamid) for 4 hours by nose-only inhalation at 4.82 mg/l gravimetric (with a mean mass median aerodynamic diameter (MMAD) of 3.87 µm (the 3 sampled values were 3.93, 3.80, and 3.87 µm) and a mean geometric standard deviation (GSD) of 2.47, respectively) followed by a 14 day observation period. All animals survived to the end of the 14 day post-exposure observation period and gained bodyweight. Clinical signs during exposure were noted in 1 female as decreased breathing at the 3.5 hour observation point. No clinical signs were noted during the 14 day post-exposure observation period. Necropsy results were unremarkable. LC50 (males and females) > 4.82 mg/l. Toxicity category IV. Acceptable. (Green, 8/12/13).

Primary eye irritation

**53207-0008 271131, "IKF-5411 Technical: Eye Irritation Study in Rabbits," (H. Ueda, The institute of Environmental Toxicology, Ibaraki, Japan, Laboratory Project ID: IET 09-0137, August 6, 2010). The left or right eyes of two groups of 3 female New Zealand White (Kbl:NZW) rabbits were treated with 0.1 g of IKF-5411 Technical (96.68% isofetamid) followed by a 72-hour observation period. Treated eyes remained unrinsed in the first group of 3 females (Group A), and treated eyes in the second group (Group B) were rinsed 30 seconds after application. Untreated eyes served as controls. No signs of irritation were indicated for the cornea or iris of any animals in Groups A and B. Hyperemia in some blood vessels (conjunctival redness scores of 1) was noted in treated eyes of all animals in both Groups A and B at 1 hour after application and had resolved completely by 48 and 24 hours after application, respectively. At 1 hour after application, very slight swelling above normal range (chemosis score of 1) was observed in the treated eye of 1 female and obvious swelling with partial eversion of lids (chemosis score of 2) was noted in the treated eyes of the other 2 females in Group A that resolved completely by 24 hours post-application. At 1 hour after application, one Group A female each was noted with a conjunctival discharge score of 1, 2, and 3, respectively, and one Group B female had a score of 1 that resolved in all 4 animals by 24 hours post-application. Eye irritation was not indicated in untreated eyes of any Group A and B animals. No treatment-related clinical signs were recorded for any animal. All animals gained bodyweight during the study. Toxicity category IV. Acceptable. (Green, 8/13/13).

Primary dermal irritation

**53207-0008 271132, "IKF-5411 Technical: Skin Irritation Study in Rabbits," (H. Ueda, The institute of Environmental Toxicology, Ibaraki, Japan, Laboratory Project ID: IET 09-0136, August 5, 2010). Three female New Zealand White (Kbl:NZW) rabbits received a single 4-hour exposure (clipped, unabraded, semi-occluded skin) to IKF-5411 Technical (96.68% isofetamid) at 0.5 g followed by a 72-hour observation period. No signs of skin irritation were indicated 1, 24, 48, or 72 hours after patch removal. Scores for erythema/eschar and edema were 0 at all time

points. During the 72-hour observation period, no treatment-related clinical signs were indicated, and all animals gained bodyweight. Toxicity category IV. Acceptable. (Green, 8/14/13).

Dermal sensitization

**53207-0008, 0056 271133, 284403, "IKF-5411 Technical: Skin Sensitization Study in Mice - Local Lymph Node Assay -" (T. Fukuyama, The Institute of Environmental Toxicology, Ibaraki, Japan, Laboratory Project ID: IET 09-0135, October 4, 2010). Twenty-five µl of IKF-5411 Technical (96.68% isofetamid) was applied to the dorsal area of both ears of 5 female CBA/JNCrlj mice per group once per day for 3 consecutive days (test days 1, 2, and 3) at 0 (dimethylformamide), 10%, 25%, and 50%. On test day six, 250 µl of sterile phosphate buffered saline (PBS) containing 20 µCi of ^{3}H-methyl thymidine was injected intravenously via the tail vein of each mouse. α hexylcinnamaldehyde (HCA) at 25% was used as positive control material. No mortality and no treatment-related clinical signs were recorded for test article or positive control animals during the study. Group mean lymph node weights for IKF-5411 Technical treated animals were comparable to vehicle control values. Group mean cellular proliferation values for test article treated animals were all comparable to vehicle control values (stimulation index (SI) values for test article treated animals were all less than 3, mean values were 1.0 at 10%, 1.1 at 25%, and 1.1 at 50%). Positive group animals had a mean SI value of 7.7, and mean lymph node weights were significantly increased compared to the vehicle control group. IKF-5411 Technical was not a dermal sensitizer in the local lymph node assay. Originally reviewed as unacceptable, possibly upgradeable with justification for not testing to a dose of 100%. (Green, 8/7/13). Record 284403 provided dosing level justification, and the study is upgraded to acceptable. (Green, 6/5/15).

SUBCHRONIC STUDIES

Rat 90-Day Oral (Feeding) Toxicity Study

**53207-0010, 0011 271135, 271137, "IKF-5411 Technical: Repeated Dose 90-Day Oral Toxicity Study in Rats," (N. Nakashima, The Institute of Environmental Toxicology, Ibaraki, Japan, Laboratory Project ID: IET 08-0088, April 15, 2011). Ten Wistar Hannover [BrlHan:WIST@Jcl(GALAS)] rats per sex per group received IKF-5411 Technical (96.61% isofetamid) in the diet at 0 (basal diet), 100, 1000, and 10000 ppm for 90 days. Group mean average test article intake levels during the study were 6.65, 68.9, and 637 mg/kg/day for males and 7.83, 78.0, and 741 mg/kg/day for females at 100, 1000, and 10000 ppm, respectively. All animals survived to scheduled sacrifice. No treatment-related changes were noted for clinical signs, physical examination results, functional observation results, bodyweight, ophthalmology, or urinalysis. Group mean food consumption was significantly reduced at the high dose level for weeks 2 and 3 in males and for weeks 3, 5, and 10 in females vs controls. Group mean activated partial thromboplastin time was significantly increased in high dose males and females and in mid dose females vs controls. At the high dose level, significant increases were noted in group mean values for gamma glutamyl transpeptidase activity in both sexes, in alanine aminotransferase activity in males, in total cholesterol in both sexes, in total protein and globulin

in both sexes, and in triglyceride in females vs controls. Gamma glutamyl transpeptidase activity was also significantly increased in mid dose males vs controls. Necropsy results included significant increases in darkening of the liver in both sexes (4/10 males and 5/10 females) at 10000 ppm vs controls. At 1000 ppm and 10000 ppm, significant increases in group mean relative liver weights were noted for both sexes and for group mean relative adrenal gland weights in females vs controls. Histology results with significantly increased incidences vs controls included: diffuse hepatocellular hypertrophy in the liver of mid-dose (8/10 males and females) and high-dose (all animals) males and females; thyroid follicular cell hypertrophy in high dose males (7/10) and females (9/10); and adrenal gland zona fasciculata cell hypertrophy in 4/10 high-dose females. Additionally, thyroid follicular cell hypertrophy was noted in 3/10 mid-dose males vs controls (ns). Record 271135 is a 28-day dietary toxicity study in rats used to determine dosing levels. NOEL = 100 ppm (6.65 mg/kg/day for males and 7.83 mg/kg/day for females) based on liver weight and histology. No adverse effect. Acceptable. (Green, 8/21/13).

Dog 90-Day Oral (Feeding) Toxicity Study

**53207-0010, 0012 271136, 271138, "IKF-5411 Technical: Repeated Dose 90-Day Oral Toxicity Study in Dogs." (R. Ohtsuka, The Institute of Environmental Toxicology, Ibaraki, Japan, Laboratory Project ID: IET 10-0015, October 18, 2011). Four Beagle dogs per sex per group received IKF-5411 Technical (96.68% isofetamid) in the diet at 0 (basal diet), 100, 1000, and 10000 ppm for 13 weeks. Group mean test article intake during the treatment period was 2.95, 29.3, and 301 mg/kg/day for males and 3.07, 32.7, and 314 mg/kg/day for females at 100, 1000, and 10000 ppm, respectively. All animals survived to scheduled termination. No treatment-related changes were noted for clinical signs, detailed clinical observations, ophthalmology, or urinalysis. Group mean bodyweight gain was comparable between control and treated groups of both sexes from week 0 to 13, except the high dose group value for males was reduced 0.9 kg vs the control (ns). Group mean food consumption was comparable between control and treated groups of both sexes from week 0 to 13, except values for high dose females were as much as ~4% lower than controls (ns) due to the failure of 2 females to eat all of the food provided. Significant increases were noted in group mean values for alkaline phosphatase activity in high dose males and females at weeks 7 and 13 and in mid dose females at week 7; for gamma glutamyl transpeptidase activity in high dose females at weeks 7 and 13; and for triglycerides in high dose males (week 13) and females (weeks 7 and 13) vs controls. Significant decreases were noted in group mean values for albumin in high dose males and females at weeks 7 and 13 and in mid dose males at week 13 and for total bilirubin in high dose females at weeks 7 and 13 vs controls. Group incidence of enlarged liver was increased for high dose males (4/4, $p \leq 0.05$) and females (3/4) and for mid dose females (1/4) vs controls. Two/4 high dose females also had dark-colored livers. Group mean absolute and relative liver weights were significantly increased for high dose males and females and for mid dose females vs controls. Treatment-related histology changes included increased centrilobular hepatocellular hypertrophy in liver of high dose males (4/4) and females (4/4) (significant for both sexes) and for 2/4 mid dose females; increased follicular cell hypertrophy in the thyroid gland of high dose males (1/4) and females (2/4); and increased zona fasciculata cell hypertrophy in the adrenal glands of 2/4 high dose males. Record 271136 is a 28-day dietary toxicity study in dogs. NOEL = 100 ppm (2.95 mg/kg/day for males and 3.07 mg/kg/day for females) based on liver weight and histology. No adverse effect. Acceptable. (Green, 8/28/13).

Rat Repeated Dosing 28-Day Dermal Toxicity Study

**53207-0013 271139, "IKF-5411 Technical: Toxicity Study by Dermal Administration to Rats (Strain CRL:CD®(SD)) for 4 Weeks," (P. B. Rees, Huntingdon Life Sciences Ltd., Alconbury, Huntingdon, Cambridgeshire, England, Laboratory Project No. JSM0147, August 18, 2011). Ten CRL:CD®(SD) rats per sex per group were dermally treated (clipped, unabraded, semi-occluded skin) with IKF-5411 Technical (96.68% isofetamid) at 0 (purified water), 100, 300, and 1000 mg/kg/day for 4 weeks (6 hours per day, 7 days per week). All animals survived to scheduled sacrifice. No treatment-related effects were indicated for clinical signs, detailed physical examinations, dermal irritation, bodyweight, food consumption, ophthalmology, hematology, serum chemistry, urinalysis, necropsy results, organ weights, or histology. Systemic NOEL (males and females) > 1000 mg/kg/day. No adverse effect. Acceptable. (Green, 9/3/13).

CHRONIC STUDIES

Chronic, rat

**53207-0014 271140, "IKF-5411 Technical: Repeated Dose 1-Year Oral Toxicity Study in Rats," (N. Nakashima, The Institute of Environmental Toxicology, Ibaraki, Japan, Laboratory Project ID: IET 09-0130, March 2, 2012). Twenty-one Wistar Hannover [BrlHan:WIST@Jcl(GALAS)] rats per sex per group received IKF-5411 Technical (96.68% isofetamid) in the diet at 0 (basal diet), 30, 100, 500, and 5000 ppm for 52 weeks. Group mean IKF-5411 technical intake during the treatment period was 1.39, 4.68, 22.7, and 237 mg/kg/day for males and 1.82, 5.92, 30.0, and 311 mg/kg/day for females at 30, 100, 500, and 5000 ppm, respectively. No treatment-related effects were indicated for clinical observations, functional observations, bodyweight, food consumption, ophthalmology, urinalysis, or gross pathology. Treatment-related hematology changes included significant prolongation in prothrombin time for high dose males and in activated partial thromboplastin time for high dose males and females vs controls. At 5000 ppm, significant increases in group mean values were recorded for gamma glutamyl transpeptidase activity in both sexes at weeks 14, 26, and 52; for total protein (weeks 14 and 26), globulin (weeks 14, 26, and 52), and triglyceride (weeks 14 and 26) in females; and for total cholesterol in males (weeks 26 and 52) and females (weeks 14) vs controls. At the high dose level, significant increases in group mean relative liver and thyroid weights were noted for both sexes vs controls. Histology results included significant increases in periportal hepatocyte fatty change and cytoplasmic eosinophilic inclusion bodies in liver of high dose males; in diffuse hepatocyte hypertrophy in liver of high dose males and females; in tubular basophilic change in kidney of high dose males; and in follicular cell hypertrophy in thyroid of high dose males and females vs controls. NOAEL = 500 ppm (22.7 mg/kg/day for males and 30.0 mg/kg/day for females) based on blood chemistry, liver and thyroid weights and histology. No adverse effect. Acceptable. (Green and Leung, 9/6/13).

Chronic, dog

**53207-0015 271141, "IKF-5411 Technical: Repeated Dose 1-Year Oral Toxicity Study in Dogs," (R. Ohtsuka, The Institute of Environmental Toxicology, Ibaraki, Japan, Laboratory Project ID: IET 10-0016, September 25, 2012). Four beagle dogs per sex per group received IKF-5411 Technical (96.68% isofetamid) in the diet at 0 (basal diet), 60, 200, and 6000 ppm for 52 weeks. Group mean IKF-5411 technical intake during the treatment period was 1.61, 5.34, and 166 mg/kg/day for males and 1.57, 5.58, and 178 mg/kg/day for females at 60, 200, and 6000 ppm, respectively. One high dose female was sacrificed *in extremis* (lateral position, decreased spontaneous motor activity, and bradypnea) at week 34 (necropsy and histology results indicated the cause was not treatment-related). No treatment-related effects were noted for clinical observations, detailed clinical observations, food consumption, or ophthalmology. Group mean bodyweight for high dose females, was reduced 10% to 14% from weeks 24 to 52 vs controls (ns). Group mean bodyweight for males was comparable to controls at all treatment levels throughout the study. Group mean serum chemistry results at the high dose level included significant increases in alkaline phosphatase activity for both sexes (weeks 13, 26, and 52) vs controls. At the high dose level, significant increases in dark liver in females, in enlarged liver in both sexes, and in group mean absolute and relative liver weights in both sexes were noted vs controls. Additionally, histology results included a significant increase in centrilobular hepatocellular hypertrophy in the livers of both sexes at the high dose level vs controls. Chronic NOEL = 200 ppm (5.34 mg/kg/day for males and 5.58 mg/kg/day for females) based on liver weight and histology. No adverse effect. Acceptable. (Green and Leung, 9/11/13).

Oncogenicity, rat

****53207-0018 271144**, "IKF-5411 Technical: Carcinogenicity Study in Rats," (N. Nakashima, The Institute of Environmental Toxicology, Ibaraki, Japan, Laboratory Project ID. IET 09-0131, December 3, 2012). Fifty one Wistar Hannover [BrlHan:WIST@Jcl(GALAS)] rats per sex per group received IKF-5411 Technical (96.68% isofetamid) in the diet at 0 (basal diet), 30, 100, 500, and 5000 ppm for 104 weeks. Group mean IKF-5411 Technical intake during the treatment period was 1.21, 4.07, 20.3, and 210 mg/kg/day for males and 1.55, 5.02, 26.1, and 263 mg/kg/day for females at 30, 100, 500, and 5000 ppm, respectively. Group mean cumulative bodyweight gain was significantly reduced in 500 ppm females for treatment weeks 16 through 80 and in 5000 ppm females for weeks 76 through 96 vs controls (male values were comparable to controls). At necropsy, significant increases in dark-colored liver were noted for high dose females surviving to terminal sacrifice (10/36 vs 0/38) and for the overall incidence for all females in the group (10/51 vs 0/51) vs controls. Also at 5000 ppm, significant increases in absolute and relative liver weights were noted for males vs controls (values for females were comparable to controls). Neoplasia was increased in the thyroid at histology. Thyroid C-cell adenoma was significantly increased for high dose male survivors at terminal sacrifice (4/43) vs controls (0/47). The overall incidence for all males in the high dose group (4/51) was not statistically significant and remained within the historical control range for the performing laboratory (1/51 to 4/51). Additionally, a significant increase in the overall group mean incidence for thyroid C-cell adenoma was noted for 30 ppm males vs controls (5/51 vs 0/51). Treatment-related non-neoplastic changes noted at the high dose level include significant increases in diffuse hepatocyte hypertrophy in liver for males (both terminal sacrifice (12/43 vs 0/47) and overall group incidence (12/51 vs 0/51)); in hepatocellular cytoplasmic eosinophilic

inclusion bodies in liver for males (both terminal sacrifice (10/43 vs 0/47) and overall group incidence (10/51 vs 0/51)); in hepatocellular brown pigment deposition in liver of females (both terminal sacrifice (9/36 vs 1/38) and overall group incidence (9/51 vs 1/51)); in thyroid follicular cell hypertrophy in both sexes (both terminal sacrifice (9/43 vs 2/47 for males and 6/36 vs 0/38 for females) and overall group incidence (9/51 vs 2/51 for males and 7/51 vs 0/51 for females)); and in the incidence of thyroid follicular cyst in terminal sacrifice males (4/43) vs controls (0/47). Chronic non-neoplastic NOEL = 500 ppm for males (20.3 mg/kg/day) and 100 ppm for females (5.02 mg/kg/day) based on liver weight, liver and thyroid histology, and bodyweight. **Possible adverse effect:** an increased incidence of thyroid C-cell adenoma in males. Acceptable. (Green and Leung, 9/25/13).

Oncogenicity, mouse

**53207-0016, 0017 271142, 271143, "IKF-5411 Technical, Carcinogenicity Study by Dietary Administration to CD-1 Mice for 78 Weeks," (K. Chase, Huntingdon Life Sciences Ltd, Alconbury, Huntingdon, Cambridgeshire, England, Report No. JSM0088, December 3, 2012). Fifty one Crl:CD-1™(ICR) BR strain CD-1 mice per sex per group received IKF-5411 Technical (96.68% isofetamid) in the diet at 0 (basal diet), 100, 800, 3000 (females only), and 4000 ppm (males only) for 78 weeks. Group mean achieved dose levels during the 78-week treatment period were 12, 92, and 502 mg/kg/day for males at 100, 800, and 4000 ppm, respectively; and 14, 118, and 431 mg/kg/day for females at 100, 800, and 3000 ppm, respectively. Group mean bodyweight gain for weeks 0 through 78 was significantly reduced for males at 4000 ppm (-18%) and females at 3000 ppm (-20%) vs controls (the significant reduction was more pronounced for weeks 9 through 78 for males (-30%) and females (-28%), respectively). At 800 ppm, group mean bodyweight gain for males was also significantly reduced (-21%) for weeks 9 through 78 vs the control although the overall value for weeks 0 through 78 was comparable to the control. The incidence of enlarged liver was increased for 4000 ppm males and for 3000 ppm females vs controls (statistically significant for females). Group mean absolute and relative liver weights were significantly increased for males at 4000 ppm and females at 3000 ppm vs controls. No treatment-related effects were noted for mortality, clinical signs, detailed physical examination results, palpable swellings, food consumption, hematology, or histology. Record 271142 is a 13-week preliminary dietary study in mice used to select dosing levels for the main study. Chronic NOEL = 100 ppm for males (12 mg/kg/day) and 800 ppm for females (118 mg/kg/day) based on bodyweight change. Carcinogenicity NOEL = 4000 ppm (502 mg/kg/day) for males and 3000 ppm (431 mg/kg/day) for females. No adverse effect. Acceptable. (Green and Leung, 9/18/13).

53207-0016 271142, "IKF-5411Technical: Preliminary Carcinogenicity Study by Dietary Administration to CD-1 Mice for 13 Weeks," (P. R. Chambers, Huntingdon Life Sciences Ltd, Alconbury, Huntingdon, Cambridgeshire, England, Report No. JSM0087, July 20, 2011). Twelve Crl:CD1(ICR) strain CD-1 mice per sex per group received IKF-5411 Technical (96.68% isofetamid) in the diet at 0 (basal diet), 100, 1000, and 8000 ppm for 78 weeks. The group mean achieved dose during the 13-week treatment period was 13, 129, and 1067 mg/kg/day for males and 16, 161, and 1306 mg/kg/day for females at 100, 1000, and 8000 ppm, respectively. All animals survived to scheduled sacrifice. No treatment-related changes were noted for clinical signs or food consumption. Bodyweight gain for both sexes at 8000 ppm was less than that of the controls over the course of the study (ns). At the end of the treatment period,

group mean hemoglobin concentration was significantly reduced for high dose females vs controls. Additionally, slight reductions (ns) in group mean hematocrit and erythrocyte count were noted for high dose males and females vs controls. At the high dose level, significant increases in group mean values were noted for alanine aminotransferase activity and urea in females vs controls at the end of the treatment period. Significant decreases were noted for albumin and the albumin/globulin ratio in high dose males and in low, mid, and high dose females; and for glucose in mid and high males vs controls after 13 weeks of treatment. Necropsy results included enlarged liver in 2/12 males and 4/12 females at 8000 ppm. Group mean absolute (adjusted using terminal bodyweight as a covariate for analysis of covariance) and relative liver weights (both sexes) and adrenal weights (females) were significantly increased at the high dose level vs controls. Treatment-related histology results were noted at the high dose level and included increases in generalized hepatocyte hypertrophy (minimal grade) in liver of males (8/12); periportal hepatocyte hypertrophy with eosinophilia (minimal grade) in liver of females (12/12); and cortical hypertrophy (minimal grade) in adrenal glands of females (6/12). NOEL = 1000 ppm (129 mg/kg/day for males and 161 mg/kg/day for females) based on liver weight and histology. No adverse effect. Supplemental data. (Green, 9/16/13) No worksheet.

GENOTOXICITY

Gene Mutation

**53207-0023 271151, "IKF-5411 Technical: Bacterial Reverse Mutation Test," (K. Wada, The Institute of Environmental Toxicology, Ibaraki, Japan, Laboratory Project ID: IET 08-0089, March 23, 2009). Triplicate cultures of *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 *uvr*A were exposed to IKF-5411 Technical (96.61% isofetamid), in the presence and absence of rat liver S9 mix, at 0 (DMSO), 61.7, 156, 185, 313, 556, 625, 1250, 1667, 2500, or 5000 μg/plate for 48 hours (at 37°C) using preincubation (cultures were treated and preincubated for 20 minutes prior to plating). Test article precipitation was noted for all strains at ≥1667 µg/plate in the presence and absence of S9 mix in the first trial and at ≥ 2500 and ≥ 1250 µg/plate in the absence and presence of S9 mix, respectively, in the second trial. 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, 10/28/13)

**53207-0023 271152, "IKF-5411 Technical: Gene Mutation Test in Mouse Lymphoma Cells," (K. Matsumoto, The Institute of Environmental Toxicology, Ibaraki, Japan, Laboratory Project ID: IET 10-0070, January 21, 2011). Duplicate cultures of L5178Y $TK^{+/-}$ mouse lymphoma cells were exposed to IKF-5411 Technical (96.68% isofetamid), in the presence and absence of rat liver S9 mix for 3 hours, at 0 (1% DMSO), 2.8, 8.3, 14.1, 25.0, 28.1, 56.3, 75.0, 112.5, and 225 μg/ml. Precipitation of the test article was observed at the highest concentration, 225 μg/ml, in the presence and absence of metabolic activation in experiments I and II. Cytotoxicity (reduced relative total growth) was demonstrated at the highest test concentrations in experiments I and II in the presence and absence of rat liver S9 mix. There were no increases in the mutant frequencies compared to the solvent controls in both experiments with and without metabolic activation. Positive controls were functional. Acceptable. (Green and Leung, 10/30/13).

**53207-0023 271152, "IKF-5411 Technical: Gene Mutation Test in Mouse Lymphoma Cells," (K. Matsumoto, The Institute of Environmental Toxicology, Ibaraki, Japan, Laboratory Project ID: IET 10-0070, January 21, 2011). Duplicate cultures of L5178Y $TK^{+/-}$ mouse lymphoma cells were exposed to IKF-5411 Technical (96.68% isofetamid), in the presence and absence of rat liver S9 mix for 3 hours, at 0 (1% DMSO), 2.8, 8.3, 14.1, 25.0, 28.1, 56.3, 75.0, 112.5, and 225 μg/ml. Precipitation of the test article was observed at the highest concentration, 225 μg/ml, in the presence and absence of metabolic activation in experiments I and II. Cytotoxicity (reduced relative total growth) was demonstrated at the highest test concentrations in experiments I and II in the presence and absence of rat liver S9 mix. There were no increases in the mutant frequencies compared to the solvent controls in both experiments with and without metabolic activation. Positive controls were functional. Acceptable. (Green and Leung, 10/30/13).

Chromosome Effects

**53207-0023 271153, "IKF-5411 Technical: Chromosome Aberration Test in Cultured Mammalian Cells," (K. Matsumoto, The Institute of Environmental Toxicology, Ibaraki, Japan, Laboratory Project ID: IET 09-132, April 5, 2010). Duplicate cultures of Chinese hamster lung fibroblasts (CHL/IU) were exposed to IKF-5411 Technical (96.68% isofetamid) at 0 (1% DMSO), 16.7, 50, 150, and 450 μg/ml for 6 hours with and 24 hours without S9 mix; at 0, 33.3, 100, 300, and 900 μg/ml for 6 hours without S9 mix; and at 0, 3.3, 10, 30, and 90 μg/ml for 48 hours without S9 mix. Cells treated for 6, 24, and 48 hours were harvested 24, 24, and 48 hours after the start of treatment, respectively. Two hours prior to harvest, colcemid solution (0.2 μg/ml) was added to each culture to arrest dividing cells in metaphase. In cultures treated for 6 hours, test article precipitation was noted without metabolic activation at 300 and 900 μg/ml and with it at 450 μg/ml. In the absence of metabolic activation, test article precipitation was observed at $\geq$ 50 μg/ml in 24-hour treatment cultures and at 90 μg/ml in 48-hour treatment cultures. Cytotoxicity (reduced relative cell growth) was demonstrated in each treatment regime. There was no increase in structural chromosome aberrations or in the number of polyploid cells after the 6-hour (-/+ S9 mix), 24-hour (-S9 mix), or 48-hour (-S9 mix) exposure periods. Positive controls were functional. Acceptable. (Green and Leung, 10/31/13).

DNA Damage

**53207-0023 271154, "IKF-5411 Technical: Micronucleus Test in Mice," (K. Matsumoto, The Institute of Environmental Toxicology, Ibaraki, Japan, Laboratory Project ID: IET 09-133, April 6, 2010). Five male Crlj:CD1 (ICR) mice per group (10 vehicle control and high dose animals per group) received a single oral gavage dose of IKF-5411 Technical (96.68% isofetamid) at 0 (0.5% methylcellulose), 500, 1000, and 2000 mg/kg followed by bone marrow sampling of 5 males per group at 24 or 48 hours post-dosing (low-dose, mid-dose and positive control animals were sampled at 24 hours only). All animals survived to scheduled sampling times, and no treatment-related clinical signs were recorded. Two thousand polychromatic erythrocytes (PCEs) per animal were analyzed by light microscopy. There was no increase in polychromatic erythrocytes (PCEs). The positive control was functional. No increase in cytogenetic damage was indicated. Acceptable. (Green and Leung, 11/1/13).

REPRODUCTIVE TOXICITY, RAT

**** 53207-0021, 0022, 0056 271149, 271150**, **284404,** "IKF-5411 Technical: Reproduction Toxicity Study in Rats (2nd Revised Final Report)," (K. Takahashi, The Institute of Environmental Toxicology, Ibaraki, Japan, Laboratory Project ID. IET 10-0023, October 30, 2012 (revised final report : January 18, 2013). Twenty-four F0 and F1 Crl:CD(SD) rats per sex per group received IKF-5411 Technical (96.68% isofetamid) in the diet at 0 (basal diet), 100, 1000, and 10000 ppm through 2 generations with 1 litter per generation. Overall group mean IKF-5411 Technical intake during premating and breeding for F0 parents was 5.76, 57.1, and 594 mg/kg/day for males and 8.85, 90.5, and 908 mg/kg/day for females, and the values for F1 parents were 6.02, 60.1, 643 mg/kg/day for males and 8.69, 89.1, and 906 mg/kg/day for females at 100, 1000, and 10000 ppm, respectively. Group mean bodyweight at 10000 ppm was significantly reduced for F0 males at treatment week 1; for F1 males at treatment weeks 0 through 5; for F0 females at treatment week 6; and for F1 females at treatment weeks 0 through 9 and on gestation days 0 through 14 vs controls (values for F0 and F1 males and females at 100 and 1000 ppm were comparable to controls). Group mean bodyweight was significantly increased for high dose F0 females at lactation day 21 vs controls. Group mean bodyweight gains at 10000 ppm were significantly reduced for F0 males during treatment weeks 0 to 1 and 0 to 2; for F1 males during treatment weeks 0 to 2 and 0 to 3; and for F0 females during treatment weeks 0 to 4, 0 to 6, 0 to 7, 0 to 8, and 0 to 9 vs controls (values for F0 and F1 males and females at 100 and 1000 ppm were comparable to controls). Group mean bodyweight gains at 10000 ppm were significantly increased for F1 females during lactation days 0 to 21 vs controls. In F0 parental animals, significant increases were noted in group mean values for absolute and relative liver weights for both sexes at 10000 ppm and for females at 1000 ppm and for absolute and relative thyroid weights for both sexes at 10000 ppm vs controls. In F1 parental animals, significant increases were noted in group mean values for absolute and relative liver weights for males at 100 and 10000 ppm (absolute values were also increased at 1000 ppm) and for females at 1000 and 10000 ppm; for absolute kidney weights for males at 100 and 1000 ppm; and for relative thyroid weights for females at 10000 ppm vs controls. At 10000 ppm, histology results included significant increases for diffuse hepatocyte hypertrophy in liver of F0 males and F1 males and females and for thyroid follicular cell hypertrophy in F0 and F1 males and females vs controls. No treatment-related effects were noted for F0 or F1 parents clinical signs, mortality, food consumption, estrous cycle length, mating indices, fertility indices, gestation indices, duration of gestation, number of implantation sites, sperm parameters, or gross pathology. Group mean F1a and F2a pup weights on lactation day 21 were significantly reduced at 10000 ppm vs controls (values were comparable to controls at all other time points and dose levels). No treatment-related effects were noted for F1a and F2a pup clinical signs, mortality, number of pups delivered, viability indices, or histology. Record 271149 is preliminary rat reproduction study used to set treatment levels for the main study. Originally reviewed as unacceptable and possibly upgradeable. Parental NOEL = 1000 ppm (57.1 and 60.1 mg/kg/day for F0 and F1 males, respectively, and 90.5 and 89.1 mg/kg/day for F0 and F1 females, respectively) based on bodyweight and bodyweight gain, liver and thyroid weight and histology. Pup NOEL = not determined. Reproductive NOEL = 10000 ppm (594 and 643 mg/kg/day for F0 and F1 males, respectively, and 908 and 906 mg/kg/day for F0 and F1 females, respectively) lack of reproductive effects. **Possible adverse effect:** syndactyly/ectrodactyly was reported for F2a pups. The study was reviewed again after submission of record 284404 ("Progeny Tests in Rats

for Elucidating Involvement of Genetic Variation in Parental Animals with a Frequently Occurred Malformation Syndrome in F2 Pups of a Reproduction Toxicity Study"). The study is upgraded to acceptable with a **possible adverse effect**: syndactyly/ectrodactyly reported in F2a pups (Green and Leung, 6/5/15).

53207-0021 271149, "IKF-5411 Technical: Reproduction Toxicity Study in Rats, Preliminary Study," (K. Takahashi, The Institute of Environmental Toxicology, Ibaraki, Japan, Laboratory Project ID: IET 10-0022, February 21, 2011). Eight Crl:CD(SD) rats per sex per group received IKF-5411 Technical (96.68% isofetamid) in the diet at 0 (basal diet), 100, 1000, 10000, and 15000 ppm from 3 weeks prior to mating through weaning of F1a offspring. Overall group mean parental IKF-5411 Technical intake during premating and breeding was 5.22, 51.9, 524, and 782 mg/kg/day for males and 9.99, 98.7, 956, and 1488 mg/kg/day for females at 100, 1000, 10000, and 15000 ppm, respectively. No treatment-related effects were noted for parental clinical signs or mortality; parental reproductive performance (estrous cycle, mating index, fertility index, gestation index, duration of gestation, number of implantation sites); pup clinical signs or mortality; number of pups delivered; pup sex ratios; pup viability; or pup gross pathology (includes unscheduled and scheduled decedents). Group mean F0 female bodyweight gain at 15000 ppm was significantly increased during lactation days 0 to 21 vs controls. F0 male bodyweight gains at all treated levels were comparable to controls. Group mean food consumption for F0 males at treatment week 5 was significantly increased at 100 and 10000 ppm vs controls (F0 male values at 1000 and 15000 ppm were comparable to controls during the study). Group mean food consumption was significantly decreased for F0 females at 10000 ppm at treatment week 1 vs controls. Significant increases were noted in group mean absolute and relative (% bodyweight) values for liver weights (F0 males and females at 10000 and 15000 ppm) and thyroid weights (F0 females at 15000 ppm) vs controls. At 1000 ppm, F0 male relative testicular weights were significantly reduced vs controls. At 10000 and 15000 ppm, significant increases in group incidence of diffuse hepatocyte hypertrophy in liver and of thyroid follicular cell hypertrophy were noted for both sexes vs controls. On lactation day 21, group mean pup weights were significantly reduced for F1a females at 10000 ppm and for F1a male and females at 15000 ppm vs controls. At 15000 ppm, male weanlings necropsied at 26 days of age had significantly increased relative brain weights vs controls (values for females were comparable to controls). Parental NOEL = 1000 ppm (51.9 mg/kg/day for males and 98.7 mg/kg/day for females) based on liver and thyroid histology. Pup NOEL = 1000 ppm based on reduced pup weights. Supplemental data. (Green, 10/3/13). No worksheet.

DEVELOPMENTAL TOXICITY

Rat

**53207-0019 271145, 271146, "IKF-5411 Technical: Embryo-Fetal Toxicity Study by Oral (Gavage) Administration to CD Rats," (D.R. Stannard, Huntingdon Life Sciences Ltd., Alconbury, Huntingdon, Cambridgeshire, England, Report No. JSM0075, October 11, 2010). Twenty-two sperm-positive female Crl:CD(SD) rats per group received IKF-5411 Technical (96.68% isofetamid) by oral gavage at 0 (0.5% sodium carboxymethylcellulose), 100, 300, and 1000 mg/kg/day on gestation days 6 through 19. All dams at 0, 100, and 300 mg/kg/day produced live litters. Twenty-one live litters were produced at 1000 mg/kg/day (1 high dose

female was sacrificed *in extremis* on gestation day 15 as a result of a dosing accident). Group mean live litter sizes were 14.7, 15.0, 14.4, and 14.3 at 0, 100, 300, and 1000 mg/kg/day, respectively. Group mean maternal absolute adjusted (adjusted for gravid uterine weight) and relative liver weights (% bodyweight) were significantly increased at 300 and 1000 mg/kg/day vs controls. There were no treatment-related effects on pregnancy rate, pre- and post implantation loss, early or late resorptions, fetal death status, percentage of male and female fetuses, fetal bodyweights, fetal external observations, fetal visceral examinations, or fetal skeletal evaluations at any treatment level. Record 271145 is a preliminary rat embryo-fetal oral toxicity (gavage) study used to determine dosing levels. Maternal NOEL = 100 mg/kg/day based on liver weights. Developmental NOEL = 1000 mg/kg/day. Teratogenicity was not indicated. Acceptable. (Green and Leung, 9/27/13).

53207-0019 271145, "IKF-5411 Technical: Preliminary Embryo-Fetal Toxicity Study by Oral (Gavage) Administration to CD Rats," (D.R. Stannard, Huntingdon Life Sciences Ltd., Alconbury, Huntingdon, Cambridgeshire, England, Report No. JSM0074, July 20, 2010). Six sperm-positive female Crl:CD(SD) rats per group received IKF-5411 Technical (96.68% isofetamid) by oral gavage at 0 (0.5% sodium carboxymethylcellulose), 100, 300, and 1000 mg/kg/day on gestation days 6 through 19. All dams survived to scheduled necropsy and were pregnant with live fetuses. A low incidence of post-dosing salivation (1 mid dose and 1 high dose dam) and chin-rubbing (3 high dose dams) was noted as a response to dose administration. Group mean maternal absolute and adjusted (- gravid uterine weight) liver weights in all treated groups were slightly higher than controls without a clear dose-response. The percentage of males per litter was reduced in a dose-related manner (56.4%, 53.4%, 44.5%, and 39.0% at 0,100, 300, and 1000 mg/kg/day, respectively). No treatment-related effects were noted for maternal bodyweight; food consumption; mean number of implantations, resorptions, live young; pre- or post-implantation losses; placental, litter, or fetal weights; or pup external macropathology. Supplemental data. (Green, 9/25/13). No worksheet.

Rabbit

**53207-0020 271147, 271148, "IKF-5411 Technical: Teratogenicity Study in Rabbits," (K. Takahashi, The Institute of Environmental Toxicology, Ibaraki, Japan, Laboratory Project ID. IET 10-0025, May 16, 2012). Twenty-five artificially inseminated female Japanese White Rabbits (Kbl:JW) received IKF-5411 Technical (96.68% isofetamid) by oral gavage at 0 (1% aqueous sodium carboxymethylcellulose), 100, 300, and 1000 mg/kg/day on gestation days 6 through 27. Twenty-four, 25, 24, and 24 live litters with mean live litter sizes of 8.3, 7.9, 8.2, and 7.8 resulted at 0, 100, 300, and 1000 mg/kg/day, respectively. Group mean maternal bodyweight gain was significantly reduced for high dose females for gestation days 6 to 9, 6 to 12, and 6 to 21 vs controls. At maternal necropsy, the incidence of pale in color liver was significantly reduced at the high dose level (0/24) vs controls (5/24). Significant increases were noted for group mean maternal absolute and relative liver weights at the high dose level vs controls. No treatment-related effects were noted for maternal clinical signs and mortality; cesarean sectioning results; fetal weights; fetal external, visceral, or skeletal malformations or variations. Record 271147 is a preliminary rabbit oral (gavage) teratogenicity study. Maternal NOEL = 300 mg/kg/day based on liver weights and bodyweight gain. Developmental NOEL = 1000 mg/kg/day. Teratogenicity was not indicated. Acceptable. (Green and Leung, 10/1/13).

53207-0020 271147, "IKF-5411 Technical: Teratogenicity Study in Rabbits Preliminary Study," (K. Takahashi, The Institute of Environmental Toxicology, Ibaraki, Japan, Laboratory Project ID. IET 10-0024, December 15, 2010). Eight artificially inseminated female Japanese White rabbits (Kbl:JW) per group received IKF-5411 Technical (96.68% isofetamid) by oral gavage at 0 (1% aqueous sodium carboxymethylcellulose), 30, 100, 300, and 1000 mg/kg/day on gestation days 6 through 27. Eight live litters were produced at 0, 30, 300, and 1000 mg/kg/day. Seven live litters were produced at 100 mg/kg/day (1 female had 1 total litter resorption). Group mean live litter sizes were 7.4, 8.6, 8.6, 8.5, and 8.6 at 0, 30, 100, 300, and 1000 mg/kg/day, respectively. No treatment-related effects were noted for maternal clinical signs, mortality, bodyweight and bodyweight change, food consumption, necropsy/cesarean section results, live fetal numbers, percentage of male and female fetuses, fetal bodyweights, or fetal external observations at any treatment level. Supplemental data. (Green, 9/30/13). No worksheet.

NEUROTOXICITY

Rat Acute Oral Neurotoxicity Study

**53207-0024 271155, "An Oral (Gavage) Acute Neurotoxicity Study of IKF-5411 in Rats," (J. D. Toot, WIL Research Laboratories, LLC, Ashland, OH., Laboratory Project No. WIL-282019, January 6, 2012 (Amended 8 March 2012)). Twelve Crl:CD(SD) rats per sex per group received a single oral gavage dose of IKF-5411 Technical (96.68% isofetamid) at 0 (1% aqueous sodium carboxymethylcellulose solution), 500, 1000, and 2000 mg/kg followed by a 14 day observation period. All animals survived to scheduled sacrifice. No treatment-related effects were noted for clinical signs, bodyweights, functional observational battery (FOB) parameters, locomotor activity, macroscopy, brain weights and measurements, or histology. Systemic NOEL = 2000 mg/kg. Neurotoxicity was not indicated. Acceptable. (Green, 10/10/13).

90-day neurotoxicity, rat

**53207-0025 271156, "A 90-Day Dietary Neurotoxicity Study of IKF-5411 in Rats," (J. D. Toot, WIL Research Laboratories, LLC, Ashland, OH., Laboratory Project No. WIL-282017, March 8, 2012). Twelve Crl:CD(SD) rats per sex per group received IKF-5411 Technical (96.68% isofetamid) in the diet at 0 (basal diet), 500, 3000, and 15000 ppm for 13 weeks. Group mean daily intake of IKF-5411 Technical during the treatment period was 34, 207, and 1049 mg/kg/day for males and 40, 245, and 1213 mg/kg/day for females at 500, 3000, and 15000 ppm, respectively. All animals survived to scheduled sacrifice. Group mean bodyweight gain was significantly reduced for high dose males and mid dose females during the first week of treatment (days 0 to 7) vs controls (values were comparable to controls at all other time points/intervals). Bodyweight for both sexes at all treatment levels was comparable to controls at all time points. No treatment-related effects were noted for food consumption, FOB parameters, locomotor activity, macropathology, brain weights and measurements, or histology. Systemic NOAEL = 15000 ppm (1049 mg/kg/day for males and 1213 mg/kg/day for females). Subchronic neurotoxicity NOAEL = 15000 ppm. No adverse effect. Acceptable. (Green, 10/14/13).

Developmental neurotoxicity, rat

Not required at this time.

Delayed neurotoxicity, hen

Not required at this time.

IMMUNOTOXICITY

Mouse 4-Week Dietary Immunotoxicity Study

**53207-0028 271162, "IKF-5411 Technical: 4 Week Dietary Immunotoxicity Study in the Female CD-1 Mouse," (P. R. Chambers, Huntingdon Life Sciences Ltd., Alconbury, Huntingdon, Cambridgeshire, UK, Laboratory Project No. JSM0205, February 29, 2012). Ten female Crl:CDI(ICR) mice per group received IKF-5411 Technical (96.68% isofetamid) in the diet at 0 (basal diet), 1000, 3000, and 7000 ppm for 4 weeks. Group mean achieved dosing levels were 197, 644, and 1380 mg/kg/day at 1000, 3000, and 7000 ppm, respectively. All animals survived to scheduled sacrifice. No treatment-related effects were noted for clinical signs, food or water consumption, or spleen and thymus weights. Group mean bodyweight gain at 1000, 3000, and 7000 ppm was 72%, 87%, and 68% of control values for study days 1 through 29 (the reduction was statistically significant at 7000 ppm). Enlarged liver was recorded for 4/10 mice at 7000 ppm vs controls (0/10) (the incidence at all other treatment levels was 0). The plaque forming cell (PFC) assay results showed no treatment-related reductions in the number of cells/spleen; PFCs/10^6 cells; or PFCs/spleen at 1000, 3000, or 7000 ppm compared to controls. The positive control group was functional. Systemic NOEL for female mice = 3000 ppm (644 mg/kg/day) based on bodyweight change. Immunotoxicity NOEL for female mice > 7000 ppm (1380 mg/kg/day). Acceptable. (Green, 10/17/13).