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

SUMMARY OF TOXICOLOGY DATA
Topramezone

Chemical Code # 6175, Document Processing Number (DPN) # 53271

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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, no adverse effect
Developmental toxicity, rat:	No data gap, no adverse effect
Developmental toxicity, rabbit:	No data gap, possible adverse effect
Developmental toxicity, mouse	No data gap, no adverse effect
Gene mutation:	No data gap, possible adverse effect
Chromosome effects:	No data gap, possible adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

All record numbers for the above study types through record 285706 in document 53271-0027 were examined.

In the 1-liners below:
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
File name: T150810 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

53271-0026 281725, "^{14}C-BAS-670 H – Study of the Biokinetics in Rats" (E. Leibold and B. van Ravenzwaay, Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, Report Project No. 02B0022/996002, May 28, 2002). Four or 12 Wistar rats (Chbb-THOM (SPF)) per sex per group received a single dose of [pyrazole-4-^{14}C] BAS 670 H or [phenyl-U-^{14}C] BAS 670 H at 10, 100, 200, 300, 400, or 500 mg/kg by oral gavage. Additionally, four rats per sex received 14 consecutive daily doses of non-radiolabeled BAS 670 H (97.8% topramezone technical) at 300 mg/kg/day by oral gavage followed by a single radiolabeled dose of [pyrazole-4-^{14}C] BAS 670 H at 300 mg/kg in an excretion/balance phase. ^{14}C-BAS-670 H was absorbed rapidly and excretion of radioactivity was mainly in the feces. Plasma levels of radioactivity peaked (Cmax) at 1 hour (Tmax) post-dosing for both sexes in all test groups. Group mean terminal half-lives (hours) were 32.7, 38.5, 30.3, 36.3, 41.1, and 40.2 hours for males and 24.0, 34.7, 20.7, 25.5, 39.9, and 35.4 hours for females at 10, 100, 100, 200, 400, and 500 mg/kg, respectively. Group mean calculated area under the plasma concentration time curve (AUC (ug Eq*hour/g)) values were 1.3, 8.4, 9.7, 14.0, 58.4, and 94.2 ug Eq*hour/g for males and 1.0, 12.4, 8.5, 24.8, 55.9, and 69.0 ug Eq*hour/g for females at 10, 100, 100, 200, 400, and 500 mg/kg respectively. In excretion/balance investigations, urine and feces were sampled at 0 to 6, 6 to 12, 12 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, 120 to 144, and 144 to 168 hours post radiolabeled dose at 10 and 300 mg/kg. The majority of radioactivity was excreted in feces (91.45% (males) and 86.02% (females) within 48 hours and 91.99% (males) and 86.71% (females) during 168 hours at 300 mg/kg and 79.75% (males) and 72.77% (females) within 48 hours and totals of 80.16% (males) and 73.08% (females) during 168 hours after 10 mg/kg). . Urinary excretion of radiolabel was 7.79% (males) and 15.64% (females) within 48 hours and 7.91% (males) and 16.04% (females) during 168 hours after 300 mg/kg, and 15.29% (males) and 28.58% (females) within 48 hours and totals of 15.68% (males) and 29.15% (females) during 168 hours after 10 mg/kg. The excretion patterns were similar for the pyrazole and phenyl radiolabels and after 14 daily doses of non-labeled BAS 670 H followed by the pyrazole radiolabel at 300 mg/kg. Group mean tissue distribution of radioactivity was determined after a single oral gavage dose of [pyrazole-4-^{14}C] BAS 670 H at 300 mg/kg and 10 mg/kg. Tissues were sampled at 1, 2, 4, and 12 hours after dosing at 300 mg/kg and at 1, 8, 18, and 22 hours after the 10 mg/kg dose. After a single dose of [pyrazole-4-^{14}C] BAS 670 H at 300 mg/kg, radioactivity levels in tissues/organs peaked at 2 hours post-dose in both sexes and declined during the following 166 hours. Highest tissue concentrations were found in G.I. tract (from 114.77 to 12484.56 ug Eq/g); liver (from 26.28 to 40.25 ug Eq/g); and kidney (from 38.07 to 66.74 ug Eq/g). After the 10 mg/kg dose, radioactivity levels in tissues peaked at 1 hour post-dosing in both sexes and declined over the following 167 hours. Highest tissue concentrations were in G.I. tract (from 12.35 to 194.36 ug

Eq/g); liver (from 2.21 to 2.56 ug Eq/g); and kidney (from 2.30 to 3.26 ug Eq/g). Using bile cannulated rats, maximum biliary excretion of radiolabel occurred during the first 3 hours after dosing at 300 mg/kg (3.35% for males and 1.61% for females) and 10 mg/kg (10.18% for males and 8.36% for females), and total biliary excretion of radiolabel during 48 hours post-dosing was 9.42% (males) and 6.69% (females) at 300 mg/kg and 31.46% (males) and 18.98% (females) at 10 mg/kg. Supplemental data. (Green, 5/7/15).

53271-0026 281726, "Metabolism of ^{14}C-Bas 670H in Rats" (N. Tilting and H.E. Knoell, BASF Aktinegesellschaft, BASF Agricultural Center Limburgerhof, Crop Protection Division, Ecology and Environmental Analytics, Limburgerhof, Germany, Study Code: 55908, December 6, 2002). Ten Wistar rats (Chbb-THOM (SPF)) per sex per group received a single oral gavage dose of [pyrazole-4-^{14}C] BAS 670H at 500 mg/kg and another 10 per sex per group received [phenyl-U-^{14}C] BAS 670H at the same dose level. Urine and feces were collected at 24 hour intervals for 4 days. Additionally, 4 Wistar rats (Chbb-THOM (SPF)) per sex per group received a single oral gavage dose of the pyrazole label at 300 mg/kg, another group of 4 per sex received the phenyl label at 300 mg/kg, and 2 more groups of 4 per sex received the same dosing regimen at 10 mg/kg. Plasma, liver, and kidneys were sampled 1 hour post-dosing. This study was performed to identify metabolites in urine, feces, plasma, bile, liver, and kidneys. To that end, samples of excreta and bile from a previous biokinetics study in rats (record 281725) were used in concert with samples produced in this study. In urine, unchanged BAS 670H was the main radioactive component, and the hydroxyl metabolite M670H02 and the cyano-metabolite M670H01 were minor components in all groups regardless of label position, dose level, or sex. Additionally, 2 other minor metabolites were detected, one, M670H13 (1-methyl-5-hydroxy pyrazole), was found in urine of dose groups that received the pyrazole label, and the other, M670H05 (BAS 670H-acid), in groups that received the phenyl label. Recoveries of radiolabeled components ranged from 5.4% to 27.4% of dose with an inverse relationship generally between the recovered amount and the dose level. In feces, unchanged BAS 670H was the main radioactive component (71.2% to 91.7% of dose), and the hydroxyl metabolite M670H02 and the cyano-metabolite M670H01 were minor components in all groups regardless of label position, dose level, or sex (except in group 6/D (phenyl label at 300 mg/kg) metabolite M670H02 was the only minor metabolite detected). In bile, unchanged BAS 670H (13.7% (males) and 10.6% (females) of dose at 10 mg/kg and 3.7% (males) and 3.4% (females) of dose at 300 mg/kg) and M670H02 (12.0% (males) and 6.5% (females) of dose at 10 mg/kg and 3.8% (males) and 2.2% (females) at 300 mg/kg) were the main radioactive components. Minor metabolites detected included M670H13 and M670H01 in both sexes at both 10 and 300 mg/kg. In liver, three minor radioactive components were detected after doses of 10 and 300 mg/kg with both the pyrazole and phenyl label: unchanged BAS 670H, M670H01, and M670H02. The total amount of identified radioactive compounds across the groups and sexes ranged from 2.1% to 2.6% of dose at 10 mg/kg and from 0.9% to 1.1% at 300 mg/kg. In kidney, the same 3 minor radioactive components, unchanged BAS 670H, M670H01, and M670H02, were detected after 10 and 300 mg/kg of both the pyrazole and phenyl labels. The total amount of identified radioactive compounds across the groups and sexes ranged from 0.6% to 1.0% of dose at 10 mg/kg and from 0.4% to 0.5% at 300 mg/kg. Radioactivity in plasma of groups V and W (doses of 10 and 300 mg/kg of the pyrazole and phenyl labels at each level) was too low (ranging from 0.06% to 0.15% of dose) for metabolite determination. A metabolic pathway was described and a schematic was included. The metabolic transformation followed 2 routes. First, oxygenation of BAS 670H to the isoxazole ring moiety (BAS 670H02) followed by ring opening and the removal of acetic acid to yield the cyano-metabolite M670H01. In the second route, BAS 670H was hydrolyzed at the methanone bridge to yield 1-methyl-5-hydroxy pyrazole (M670H13) and BAS 670H-acid (M670H05). Supplemental data. (Green, 5/14/15).

The two rat metabolism studies above are each supplemental data and, taken together, complete the data requirements for metabolism.

GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT

Acute oral toxicity, rat

**53721-0006 281670, "BAS 670 H: Acute Oral Toxicity in Rats" (A.O. Gamer and H.D. Hoffman, Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, Report Project No. 10A0124/981129, June 26, 2000). In the first dosing step, one group of 3 male Wistar (chbb: thom) rats received a single oral gavage dose of BAS 670 H (97.7% topramezone technical) at 2000 mg/kg (a group of 3 females was dosed in a second step) followed by a 14-day observation period. Food was withheld 16 hours prior to dosing and necropsy. No treatment-related clinical signs were recorded. All animals survived through the 14-day observation period and gained bodyweight. Necropsy results were unremarkable. LD_{50} (M & F) > 2000 mg/kg. Toxicity category III. Acceptable. (Green, 2/25/15).

**53271-0006 281671, "BAS 670 H – Acute Oral Toxicity Study in Wistar Rats" (A.O. Gamer and E. Leibold, Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, Report Project No. 10A0124/981143, December 9, 2002). In the first dosing step, 1 group of 3 fasted female Wistar (CrlGlxBrlHan:WI) rats received a single oral gavage dose of BAS 670 H (95.8% topramezone technical) at 2000 mg/kg (another group of 3 females was dosed in a second step) followed by a 14- observation period. No treatment-related clinical signs were observed. All animals survived through the 14-day observation period and gained bodyweight. Necropsy results were unremarkable. LD_{50} (F) > 2000 mg/kg. Toxicity category III. Acceptable. (Green, 2/25/15).

**53271-0006 281672, "BAS 670 H – Acute Oral Toxicity Study in Wistar Rats" (A.O. Gamer and J. Hellwig, Department of Toxicology of BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, Report Project No.10A0124/981145, December 18, 2002). In the first dosing step, 1 group of 3 fasted female Wistar (CrlGlxBrlHan:WI) rats received a single oral gavage dose of BAS 670 H (99.3% topramezone technical) at 2000 mg/kg (another group of 3 females was dosed in a second step) followed by a 14- observation period. There were no treatment-related clinical signs or gross pathology results. All animals survived through the 14-day observation period and gained bodyweight. LD_{50} (F) > 2000 mg/kg. Toxicity category III. Acceptable. (Green, 2/26/15).

Acute dermal toxicity

**53271-0006 281673, "BAS 670 H: Acute Dermal Toxicity in Rats" (A.O. Gamer and H.D. Hoffman, Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, Report Project No. 11A0124/981130, June 26, 2000). Five Wistar (chbb: thom) rats per sex received a single 24 hour dermal exposure (clipped, unabraded, semi-occluded skin) to BAS 670 H (97.7% topramezone technical) at 2000 mg/kg followed by a 14 day observation period. All animals survived to the end of the observation period with no treatment-related clinical signs or necropsy findings. One female had very slight erythema at the treatment site on day 1 after patch removal that cleared by the next observation. All animals gained bodyweight during the study. LD_{50} (M & F) > 2000 mg/kg. Toxicity category III. Acceptable. (Green, 2/26/15).

**53271-0006 281674, "BAS 670 H: Acute Dermal Toxicity Study in Rats" (A.O. Gamer and E. Leibold, Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, Report Project No. 11A0124/981144, December 9, 2002). Five Wistar (CrlGlxBrlHan:WI) rats per sex received a single 24 hour dermal exposure (clipped, unabraded, semi-occluded skin) to BAS 670 H (95.8% topramezone technical) at 2000 mg/kg followed by a 14 day observation period. All animals survived to the end of the observation period with no treatment-related clinical signs or necropsy findings. Skin effects at the treatment sites on day 1 after patch removal included very slight erythema in 1 female, well-defined erythema in 2 males and 3 females, moderate to severe erythema in 2 males, and scaling in 5 females that all cleared by day 7. Yellow discoloration at the application sites was present in all animals at day 1, 7, and 14. All animals gained bodyweight during the study. LD_{50} (M & F) > 2000 mg/kg. Toxicity category III. Acceptable. (Green, 2/27/15).

**53271-0006 281675, "BAS 670 H – Acute Dermal Toxicity Study in Rats" (A.O. Gamer and J. Hellwig, Department of Toxicology of BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, Report Project No.11A0124/981146, December 18, 2002). Five Wistar (CrlGlxBrlHan:WI) rats per sex received a single 24 hour dermal exposure (clipped, unabraded, semi-occluded skin) to BAS 670 H (99.3% topramezone technical) at 2000 mg/kg followed by a 14-day observation period. All animals survived to the end of the observation period with no treatment-related clinical signs or necropsy findings. One male had very slight erythema at the treatment site after patch removal on study day 1 that cleared by the next observation (day 7). All animals gained bodyweight during the study. LD_{50} (M & F) > 2000 mg/kg. Toxicity category III. Acceptable. (Green, 2/27/15).

Acute inhalation toxicity, rat

**53271-0006 281676, "BAS 670 H – Acute Inhalation Toxicity Study in Wistar Rats, 4-Hour Exposure" (A.O. Gamer and H.D. Hoffmann, Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, Report Project No. 13l0124/987024, September 4, 2000). Five Wistar (Crl:WI (GLX/BRL/HAN)IGS BR) rats per sex were exposed to BASF 670 H (95.8% topramezone technical) for 4 hours at 5.05 mg/l analytical (with mean mass median aerodynamic diameters (MMAD) of 5.3 and 4.8 um and mean geometric standard deviations (GSD) of 3.6 and 3.3, respectively) followed by a 14-day observation period. Clinical signs that began during exposure included accelerated respiration, squatting posterior, piloerection, and smeared fur in all animals. All animals appeared normal from study day 5 to necropsy. All animals gained bodyweight during the study, and necropsy results were unremarkable. LC_{50} (M & F) > 5.05 mg/l. Toxicity category IV. Acceptable. (Green, 3/2/15).

53271-0006 281677, **"BAS 670 H – Acute Inhalation Toxicity study in Wistar Rats, 4-H Dust Exposure" (L. Ma and E. Leibold, Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, Report Project No. 13l0124/987026, November 27, 2002). Five Wistar (CrlGlxBrlHan:WI) rats per sex were exposed to BAS 670 H (98.7% topramezone technical) for 4 hours at 5.4 mg/l analytical (with mean mass median aerodynamic diameters (MMAD) of 3.2 and 3.9 um and mean geometric standard deviations (GSD) of 3.4 and 3.6, respectively) followed by a 14-day observation period. Visually accelerated respiration was noted in 3 males and 5 females from the beginning of treatment through post exposure day 1 and in 2 males from the beginning of treatment through post-exposure day 4. Salivation and smeared fur were noted in all animals from the start of treatment to post exposure day 1. All animals survived to the end of the 14 day exposure period. All animals, except one female, gained bodyweight during the study. LC_{50} (M & F) > 5.4 mg/l. Toxicity category IV. Acceptable. (Green, 3/2/15).

Primary eye irritation, rabbit

**53271-0006 281678, "BAS 670 H: Acute Eye Irritation in Rabbits" (C. Wiemann and J. Hellwig, Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, Report Project No. 11H0124/982237, June 5, 2000). The right eyes of 1 male and 2 female White New Zealand (Hsdlf: NZW) rabbits were treated with 0.1 ml (40 mg) of BAS 670 H (97.7% topramezone technical) followed by a 7 day observation period. Eyes were rinsed with tap water 24 hours after test article application. Conjunctival redness was noted in treated eyes of all animals through 72 hours after treatment. All animals had scores of 2 (moderate) at 1 and 24 hours, two had scores of 2 and one had a score of 1 (slight) at 48 hours, all animals had scores of 1 at 72 hours, and all eyes were clear (scores of 0) by day 7. Chemosis scores of 2 were noted in all animals at 1 hour and in one animal at 24 hours, and scores of 1 were noted in 2 animals at 24 hours and in one rabbit at 48 hours, and all eyes were clear at 72 hours. Discharge scores of 1 were noted in 3 animals at 1 hour and in 2 animals at 24 hours, and all eyes were clear at 48 hours. Corneal opacity and iritis were not indicated. Toxicity category III. Acceptable. (Green, 3/3/15).

**53271-0006 281679, "BAS 670 H – Acute Eye Irritation in Rabbits" (M. Remmele and E. Leibold, Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, Report Project No. 11H0124/982290, December 9, 2002). The right eyes of 1 male and 2 female New Zealand White rabbits (A1077 INRA) were treated with 0.1 ml (43 mg) of BAS 670 H (95.8% topramezone technical) followed by a 7 day observation period. Eyes were rinsed with tap water 24 hours after application. Conjunctival redness was noted in treated eyes of animals through 72 hours post-treatment. All animals had moderate redness (scores of 2) at 1 hour, two animals had scores of 2 and one had a score of 3 (severe) at 24 hours, one animal had a score of 2 at 48 hours, and two animals had scores of 1 (slight) at 48 and 72 hours, eyes were clear (score of 0) in 1 animal at 72 hours and in the other two rabbits at 7 days. Slight conjunctival chemosis (score of 1) was noted in 2 animals at 1 hour and in one animal at 24 hours, and all treated eyes were clear at 48 hours. Slight discharge (score of 1) was noted in all 3 animals at 1 hour, and all eyes were clear at 24 hours. Corneal opacity and iritis were not indicated. Toxicity category III. Acceptable. (Green, 3/4/15).

**53271-0006 281680, "BAS 670 H, Acute Eye Irritation in Rabbits" (M. Remmele and J. Hellwig, Department of Toxicology of BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, Report Project No. 11H0124/982293, December 18, 2002). The right eyes of 1 male and 2 female New Zealand White rabbits (A1077 INRA) were treated with 0.1 ml (58 mg) of BAS 670 H (99.3% topramezone technical) followed by a 72 hour observation period. Eyes were rinsed with tap water 24 hours after test article application. Slight (score of 1) to moderate (scores of 2) conjunctival redness was noted in 1 and 2 animals, respectively at 1 hour and 24 hours after treatment, and two animals had scores of 1 and one had a score of 0 (clear) at 48 hours, and all eyes were clear at 72 hours. Slight chemosis was noted in 2 animals and the other animal had clear eyes at 1 hour, and all eyes were clear at 24 hours. Slight discharge was noted in all 3 animals at 1 hour, and all eyes were clear at 24 hours. Corneal opacity and iritis were not indicated. Toxicity category III. Acceptable. (Green, 3/4/15).

Primary dermal irritation

**53271-0006 281681, "BAS 670 H: Acute Dermal Irritation/Corrosion in Rabbits" (C.Wiemann and J. Hellwig, Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, Report Project No. 18H0124/982236, June 5, 2000). One male and 2 female New Zealand White rabbits (Chbb:NZW) received a single 4-hour exposure (clipped, unabraded, semi-occluded skin) to BAS 670 H (97.7% topramezone technical) at 0.5 g. Very slight erythema (score of 1) was noted in 2 animals (1 animal had a score of 0 (clear)) at 1

hour and in 1 animal at 24 and 48 hours (the other 2 animals were clear). All treatment sites were clear at 72 hours. Edema scores were 0 for all animals at all time points. Toxicity category IV. Acceptable. (Green, 3/5/15).

**53271-0006 281682, "BAS 670 H – Acute Dermal Irritation/Corrosion in Rabbits" (M. Remmele and E. Leibold, Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, Report Project No. 18H0124/982289, December 9, 2002). One male and 2 female New Zealand White rabbits (A1077 INR) received a single 4-hour exposure (clipped, unabraded, semi-occluded skin) to BAS 670 H (95.8% topramezone technical) at 0.5 g. Very slight erythema (score of 1) was noted in 1 animal at 1 hour and in 2 animals at 24 hours (1 animal had a score of 0 (clear)), and in 1 animal at 48 hours (2 animals were clear). Well-defined erythema (score of 2) was noted in 2 animals at 1 hour. All animals were clear at 72 hours. Edema scores for all animals were 0 at all time points. Toxicity category IV. Acceptable. (Green, 3/5/15).

**53271-0006 281683, "BAS 670 H, Acute Dermal Irritation/Corrosion in Rabbits" (M. Remmele and J. Hellwig, Department of Toxicology of BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, Report Project No. 18H0124/982292, December 18, 2002). One male and 2 female New Zealand White rabbits (A1077 INR) received a single 4-hour exposure (clipped, unabraded, semi-occluded skin) to BAS 670 H (99.3% topramezone technical) at 0.5 g. Very slight erythema (score of 1) was noted in all 3 animals at 1 hour after patch removal, and all animals were clear (score of 0) at 24, 48 and 72 hours. Edema scores were 0 for all animals at all time points. Toxicity category IV. Acceptable. (Green, 3/5/15).

Dermal sensitization

**53271-0006 281684, "BAS 670 H – Maximization Test in Guinea Pigs" (C. Wiemann and J. Hellwig, Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, Report Project No. 30H0124/982238, June 6, 2000). Female guinea pigs (Hsd Poc : DH) were used. The study included 2 groups of 10 control animals each and 1 main test group of 20 animals. A second control group was used as a naïve reserve in case a second challenge was needed as a result of borderline results at the first challenge. A second challenge was not needed. 1% Tylose CB 30.000 (aqueous sodium carboxymethylcellulose) was used as the vehicle control. Intense erythema and swelling (scores of 3) were observed at the intradermal injection sites of all control (group 1 and 2) and test group sites that received Freund's Adjuvant (FA)/0.9% in aqueous sodium chloride (1:1); in all test group animals that received injections of 5% BAS 670 H (97.7% topramezone technical) in FA/0.9% aqueous sodium chloride (1:1); and in all control animals (group 1 and 2) that received injections of a 50% mixture of 1% Tylose CB 30.000 in FA/ 0.9% in aqueous sodium chloride (1:1) . After the injection of 5% BAS 670 H in 1% Tylose CB 30.000, all test group animals showed moderate and confluent erythema (scores of 2). Control group animals (group 1 and 2) injected with 1% Tylose CB 30.000 showed no skin reaction (scores of 0). No skin reactions were observed (scores of 0) in any control group 1 animals or test group animals after topical challenge with 25% BAS 670 H in 1% Tylose CB 30.000. All animals in both control groups and in the test group gained bodyweight during the study. BAS 670 H was not a skin sensitizer in the guinea pig maximization test. Acceptable. (Green, 3/9/15).

**53271-0006 281685, "BAS 670 H – Maximization Test in Guinea Pigs" (A.O. Gamer and E. Leibold, Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, Report Project No. 30H0124/982291, December 9, 2002). Female guinea pigs (Hsd Poc : DH) were used with BAS 670 H (95.8% topramezone technical). The study included 2 groups of 10 control animals each and 1 main test group of 20 animals. A second control group

was used as a naïve reserve in case a second challenge was needed as a result of borderline results at the first challenge. A second challenge was not needed. 1% sodium carboxymethylcellulose in doubly distilled water was used as the vehicle control. Intense erythema and swelling (scores of 3) were observed at the intradermal injection sites of all control (group 1 and 2) and test group sites that received Freund's Adjuvant (FA)/0.9% in aqueous sodium chloride (1:1); in all test group animals that received injections of 5% BAS 670 H in FA/0.9% aqueous sodium chloride (1:1); and in all control animals (group 1 and 2) that received injections of a 50% mixture of 1% CMC in doubly distilled water in FA/ 0.9% in aqueous sodium chloride (1:1). After the injection of 5% BAS 670 H in 1% CMC in doubly distilled water, all test group animals showed moderate and confluent erythema (scores of 2) with swelling. Control group animals (group 1 and 2) injected with 1% CMC in doubly distilled water showed no skin reaction (scores of 0). No skin reactions were observed (scores of 0) in any control group 1 animals or test group animals after topical challenge with 25% BAS 670 H in 1% CMC in doubly distilled water at 24 and 48 hours after patch removal. All animals in control group 1 and in the test group gained bodyweight during the study (control group 2 animals were not weighed at the end of the study). BAS 670 H was not a skin sensitizer in the guinea pig maximization test. Acceptable. (Green, 3/10/15).

**53271-0006 281686, "BAS 670 H – Maximization Test in Guinea Pigs" (A.O. Gamer and J. Hellwig, Department of Toxicology of BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, Report Project No. 30H0124/982294, December 18, 2002). Female guinea pigs (Hsd Poc : DH) were used with BAS 670 H (99.3% topramezone technical). The study included 2 groups of 10 control animals each and 1 main test group of 20 animals. A second control group was used as a naïve reserve in case a second challenge was needed as a result of borderline results at the first challenge. 1% sodium carboxymethylcellulose (CMC) in doubly distilled water was used as the vehicle control. Intense erythema and swelling (scores of 3) were observed at the intradermal injection sites of all control (group 1 and 2) and test group sites that received Freund's Adjuvant (FA)/0.9% in aqueous sodium chloride (1:1); in all test group animals that received injections of 5% BAS 670 H in FA/0.9% aqueous sodium chloride (1:1); and in all control animals (group 1 and 2) that received injections of a 50% mixture of 1% CMC in doubly distilled water in FA/ 0.9% in aqueous sodium chloride (1:1). After the injection of 5% BAS 670 H in 1% CMC in doubly distilled water, all test group animals showed moderate and confluent erythema (scores of 2) with swelling. Control group animals (group 1 and 2) injected with 1% CMC in doubly distilled water showed no skin reaction (scores of 0). No skin reactions were observed (scores of 0) in any control group 1 animals or test group animals after topical challenge with 25% BAS 670 H in 1% CMC in doubly distilled water at 24 and 48 hours after patch removal. A second challenge using control group animals was not performed. All animals in control group 1 and in the test group gained bodyweight during the study (control group 2 animals were not weighed at the end of the study). BAS 670 H was not a skin sensitizer in the guinea pig maximization test. Acceptable. (Green, 3/10/15).

SUBCHRONIC STUDIES

Rat Subchronic Oral Toxicity Studies

53271-0009 281690, "BAS 670H – Subchronic toxicity study in Wistar Rats; Administration in the Diet for 3 months"; supp; Wistar Rat; Experimental Toxicology and Ecology, BASF Aktiengesellschaft, 67056 Ludwigshafen/Rhein, Germany, Kaspers, U., Laboratory Project ID:

50S0124/98168, BASF Registration Document # 2003/1006252, 3/10/2003; BAS 670H, Batch No. 30786/22, 99.3% pure, a beige solid was administered to 10 Wistar Rats/sex by diet at 0, 15, or 30 ppm [mean test substance intake: 0, 1.1, and 2.1 mg/kg/day for males; 0, 1.3, 2.5 mg/kg/day for females, respectively] for 3 months. Animals were observed for general condition, along with detailed clinical examinations, hematology, blood chemistry, pathology and histopathology. No mortality except for 1 female from 15 ppm group which was found dead on day 77. Moderate paled skin, hypothermia, severe head edema, moderate to severe reduction of general condition was observed before the rat was found dead. No test substance treatment related changes in body weight, bodyweight gains, food consumption, hematology, blood chemistry, and ophthalmology in both males and females were observed. Increased relative liver weight in groups 1 and 2 males and group 2 females, increased relative kidney weight in group 2 males, increased high ketone content in urine from group 2 males and females, increased diffuse degeneration of pancreas in group 2 males, increased flaky colloid in thyroid gland in groups 1 and 2 males and group 2 females was observed. **NOEL (No Observed Effect Level)** for systematic toxicity for male rats: = 15 ppm (1.1 mg/kg/day) and female rats: 15 ppm (1.3 mg/kg/day) due to organ weights and microscopic findings. **Supplemental** (Pan& Leung, 4/3/2015).

53271-0010 281691, "Reg. No. 388010: Range finding Study in Wistar Rats; Administration in the Diet for 4 weeks"; 821; Rat; Experimental Toxicology and Ecology, BASF Aktiengesellschaft, 67056 Ludwigshafen/Rhein, Germany, Mellert, W., Laboratory Project ID: 30S0362/98137, BASF Registration Document # 2001/1017171, 10/8/2001; BAS 670H, Batch No. N 26, 95.8% pure, a beige solid was administered to 5 rats/sex by diet at 0, 100, 500, 3000, or 12800 ppm [mean test substance intake: 9.4, 47.2, 283.9 and 1197.3 mg/kg/day for males; 10.2, 51.5, 312.3 and 1304.4 mg/kg/day for females of 100, 500, 3000, and 12800 ppm groups, respectively] for 4 weeks. Animals were observed for clinical signs and mortality. Hematological, clinical chemical examinations and urinalysis were conducted near the end of the administration period. Gross pathology and histopathological examinations of liver and kidneys were assessed. No mortality. No test substance treatment related changes in body weight, bodyweight gains, food consumption, hematological examinations, urinalysis, organ weight, gross pathology and histopathological examinations of liver and kidneys in both males and females were observed. Increased tyrosine level in high dose group males and females at the end of the treatment period was observed. **NOEL (No Observed Effect Level)**: 3000 ppm (283.9 and 312.3 mg/kg/day for male rats and female rats, respectively). **Supplemental**. (Pan& Leung, 4/6/2015).

Mouse Subchronic Oral Toxicity Study

**53271-0009 281689, "BAS 670H – Subchronic oral toxicity study in C57BL mice: Administration in the Diet for 3 months"; 831; mice; Experimental Toxicology and Ecology, BASF Aktiengesellschaft, 67056 Ludwigshafen/Rhein, Germany, Mellert, W., Laboratory Project ID: 60C0124/98096, BASF Registration Document # 2000/1017246, 10/17/2000; BAS 670H, Batch No. N 14, 97.7% pure, a beige solid was administered to 10 mice/sex by diet at 0, 125, 1000, or 8000 ppm [mean test substance intake: 0, 37, 288, and 2289 mg/kg/day for males; 0, 51, 406 and 3010 mg/kg/day for females, respectively] for 3 months. Animals were observed for general condition, detailed clinical examinations, hematology, blood chemistry, pathology

and histopathology. One high dose female died prematurely (not treatment-related). No test substance treatment related changes in body weight, bodyweight gains, food consumption, hematology, blood chemistry, pathology and histopathology in both males and females were observed. Increased relative liver weight in groups 2 and 3 females at necropsy was not treatment related due to absence of histopathological findings. **NOEL (No Observed Effect Level)**: for male and female mice: 8000 ppm (2298 and 3010 mg/kg/day for male mice and female mice, respectively) due to no treatment related effects at HDT. **Acceptable** (Pan& Leung, 3/20/2015).

Dog Subchronic Oral toxicity Study

**53271-0011 281692, "BAS 670 H – Subchronic Oral Toxicity Study in Beagle Dogs, Administration in the Diet for 3 Months" (U. Kaspers *et al*., Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, Report Project No. 31D0124/98110, May 23, 2002). Five purebred Beagle dogs per sex per group received BAS 670 H (95.2% to 95.8% topramezone technical) in the diet at 0 (basal diet), 3000, 9000, and 25000 ppm for 3 months. Group mean test article intake during the treatment period was 182, 535, and 1511 mg/kg/day for males and 205, 624, and 1712 mg/kg/day for females at 3000, 9000, and 25000 ppm, respectively. All animals survived to scheduled termination. Treatment-related effects were noted at 25000 ppm. Group mean bodyweight gain was reduced for high dose males throughout the treatment period. Values were as little as 1/16th (6.25%) of control values (0.1 kg vs 1.6 kg) on study day 70, and mean bodyweight gain was 0.2 kg (33.33%) for high dose males on study day 91 vs 1.9 kg for controls, however, statistical significance was only indicated at day 21 (0.1 kg treated (16.67%) vs 0.6 kg controls). Female bodyweight gain was not affected by treatment at the high dose level. Light-brown discolored feces were noted for both sexes at 25000 ppm consistently throughout the treatment period. Additionally, two high-dose males had red-brown discolored urine between study days 67 and 87. No treatment-related effects were noted for ophthalmology, food consumption, hematology, serum chemistry, urinalyses, organ weights, gross pathology, or histology results at any treated level. NOEL (M & F) = 9000 ppm (535 mg/kg/day for males and 624 mg/kg/day for females) based on clinical signs. No adverse effect. Acceptable. (Green, 3/16/15).

Rat Repeated Dosing 28-Day Dermal Toxicity Study

**53271-0011 281693, "BAS 670 H – Repeated Dose Dermal Toxicity Study in Wistar Rats" (U. Kaspers et al., Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, Report Project No. 33S0124/98149, August 16, 2002). Ten Wistar rats (CrlBlxBrlHan:WI) per sex per group were dermally treated (clipped, unabraded, semi-occluded skin) with BAS 670 H (95.8% topramezone technical) at 0 (aqueous 0.5% CMC), 100, 300, and 1000 mg/kg/day for 4 weeks (6 hours per day, 5 days per week). All animals survived to scheduled sacrifice. No treatment-related effects were noted for clinical signs, detailed clinical examinations, dermal irritation, bodyweight, food consumption, water consumption, ophthalmology, or hematology at 100, 300, or 1000 mg/kg/day for either sex compared to controls. Group mean serum chloride was significantly decreased in all treated males compared to controls. Significant increases in group mean values were noted for relative liver weights in low, mid, and high dose males and for relative thymus weight in high dose males compared to controls. Histology results included an increase in slight (grade 2) follicular cell hypertrophy of the thyroid gland. The incidence was 3, 2, 6, and 7 for males and 0, 0, 0, and 2 for females at 0, 100, 300, and 1000 mg/kg/day, respectively. Systemic NOEL for males = 100 mg/kg/day and for females = 300 mg/kg/day based on thyroid gland histology results. No adverse effect. Acceptable. (Green, 3/18/15).

CHRONIC STUDIES

Chronic, rat

**53271-0014 281696, "BAS 670 H – Chronic Toxicity Study in Wistar Rats, Administration via the Diet for 12 Months" (U. Kaspers et al., Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, Report Project No. 70S0124/98098, December 12, 2002). Twenty Wistar rats (CrlGlxBrlHan:WI) per sex per group received BAS 670 H (Batch Numbers N 17 and N26 (95.2% and 95.8% topramezone technical, respectively)) in the diet at 0 (basal diet), 6, 60, 600, and 6000 ppm for 12 months. Group mean test article intake during the study was 0.4, 3.9, 42.0, and 422.6 mg/kg/day for males and 0.5, 5.3, 53.2, and 535.0 mg/kg/day for females at 6, 60, 600, and 6000 ppm, respectively. Treatment-related clinical observations during the study included an increased incidence of corneal opacity (of the right or left eye or of both eyes) in males and females at 60, 600, and 6000 ppm compared to controls. The corneal opacity incidence during the study was 0, 3, 9, and 11 for males and 1 (diagnosed as opacity of the lens in this animal, hence not treatment-related), 4, 15, and 17 for females at 6, 60, 600, and 6000 ppm, respectively. Significant increases were noted in group mean relative values for liver weights for males and females and for kidney and testes weights for males at 60, 600, and 6000 ppm compared to controls (kidney weights were also significantly increased for high dose females). At necropsy, 0, 0, 3, 9, and 11 males and 0, 0, 4, 14, and 17 females at 0, 6, 60, 600, and 6000 ppm, respectively showed cloudiness of the cornea. At histology, the cloudiness of the cornea corresponded to chronic purulent keratitis. The incidence was 0, 0, 3, 9, and 11 in males and 0, 0, 4, 13, and 16 in females at 0, 6, 60, 600, and 6000 ppm, respectively. The keratitis was unilateral in most males and affected both eyes in most females. Histology of the thyroid glands revealed a minimal to slight dose-related increase in diffuse hypertrophy of follicular epithelium in males. The incidence was 1, 2, 6, 11, and 13 in males and 0, 0, 0, 0, and 0 in females at 0, 6, 60, 600, and 6000 ppm, respectively. The incidence of thyroid focal follicular cell hyperplasia was 1, 1, 6, 4, and 7 for males and 0, 0, 0, 1, and 2 in females at 0, 6, 60, 600, and 6000 ppm, respectively. In the pancreas, an increase in diffuse degeneration of acinar cells was noted for males. The incidence was 3, 2, 4, 11, and 13 in males and 2, 3, 1, 2, and 1 in females at 0, 6, 60, 600, and 6000 ppm, respectively. NOAEL = 6 ppm (0.4 mg/kg/day for males and 0.5 mg/kg/day for females) based on eye effects and liver weights. No adverse effect. Acceptable. (Green and Leung, 4/2/15).

Chronic, dog

**53271-0012 281694, "BAS 670 H – Chronic Oral Toxicity Study in Beagle Dogs, Administration in the Diet for 12 Months" (U. Kaspers et al., Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, Report Project No. 33D0124/98123, December 4, 2002). Five purebred Beagle dogs per sex per group received BAS 670 H (95.8% topramezone technical) in the diet at 0 (basal diet), 3000, 9000, and 25000 ppm for 12 months. Bodyweight development was less than expected in all groups, including controls, during the study. Subsequently, from study day 210 onwards, the daily food ration of 350 g/animal was increased to 400 g/animal, resulting in new dietary concentrations of 0, 2600, 7800, and 22000 ppm. Group mean test article intake during the entire study was 81, 248, and 688 mg/kg/day for males and 92, 287, and 780 mg/kg/day for females at 3000/2600, 9000/7800, and 25000/22000 ppm, respectively. One high dose male was found dead on study day 137,

and the cause of death was determined as hypovolemic/endotoxic shock after a necrotizing cystitis and uremia. The male had vomitus (study day 131), diarrhea (study day 131, 133 to 136), reduced general condition (moderate on study day 135, severe on day 136), and abdominal and lateral position on study day 136. Another high dose male showed lateral position, slight tremor, hypothermia, slight apathy, diarrhea (partly bloody), moderate polyuria, and unsteady gait on study day 280 and was sacrificed. Histology revealed severe hemorrhagic and necrotizing cystitis in both animals. A complete transmural necrosis of the bladder wall with high accumulation of inflammatory cells, fibrin, hemorrhage and debris affecting all layers of the wall was noted. Group mean bodyweight change for low, mid, and high dose males was reduced (but never reached statistical significance) during the entire treatment period, resulting in bodyweight loss and/or reduced bodyweight gain from study days 7 to 210. The effects on bodyweight change were lessened after the increase in food provided from study day 210 on, but the effects were still present at the end of the treatment period in all groups. In low, mid, and high dose females, bodyweight gain was also impaired during the entire treatment period with statistical significance on study day 133 at the low dose; on days 77, 91 to 259, 315, and 329 to 364 at the mid dose level; and on days 161, 175, and 238 at the high dose level compared to controls. Increased ketone concentrations (not statistically significant) were noted in urine samples of all males and females at the low, mid, and high dose levels taken during the treatment period compared to controls. The mode of action of the test article is inhibition of the enzyme p-hydroxyphenylpyruvate-dioxygenase, an enzyme involved in tyrosine catabolism in animals. Blocking the enzyme results in increased tyrosine levels in the blood and urine of treated animals and leads to excretion of large amounts of p-hydroxyphenylpyruvic acid via the urine. P-hydroxyphenylpyruvic acid, a keto-acid, interferes with the reagent of the test strip method and causes false-positive results for ketone bodies in urine specimens. Results of urinary sediment evaluation included crystals of parent compound in high dose males (5/5 and 3/3 at 3 and 12 months, respectively) and females (4/5 and 2/5 at 3 and 12 months, respectively) and in 2/5 mid dose females at 12 months. Additionally, slightly decreased pH values (< 6.0) that are possibly related to crystal precipitation were noted for males and females in all dose groups compared to controls, and females were more affected than males. Chronic NOEL (M & F) < 2600 ppm (81 mg/kg/day for males and 92 mg/kg/day for females) based on reduced bodyweight change and urinary effects. No adverse effect. Acceptable. (Green and Leung, 3/24/15).

53271-0013 281695, “BAS 670 H – Supplementary Chronic Oral Toxicity Study in Beagle Dogs, Administration in the Diet for 12 Months” (U. Kaspers et al., Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, Report Project No. 33D0124/98144, December 20, 2002). Five purebred Beagle dogs per sex per group received BAS 670 H (95.8% topramezone technical) in the diet at 0 (basal diet), 100, and 500 ppm for 12 months. Group mean test article intake during the study was 2.9 and 15.3 mg/kg/day for males and 3.1 and 15.4 mg/kg/day for females at 100 and 500 ppm, respectively. Group mean bodyweight change for 500 ppm males was reduced (but never reached statistical significance) during the entire treatment period, resulting in bodyweight loss on study day 7 and reduced bodyweight gain (mean reductions of 9.1% to 47.0%) from study days 14 to the end of the treatment period compared to controls. No treatment-related effects were indicated for clinical signs, mortality, food consumption, ophthalmology, hematology, serum chemistry, organ weights, necropsy results, or histology in any treatment group animals compared to controls. Chronic NOEL for males = 100 ppm (2.9 mg/kg/day) based on bodyweight loss/reduced gain. Chronic NOEL for females = 500 ppm (15.4 mg/kg/day). No adverse effect. Supplemental data to record 281694. (Green and Leung, 3/25/15).

Oncogenicity, rat

****53271-0017 281701**, "BAS 670 H – Carcinogenicity Study in Wistar Rats, Administration in the Diet for 24 Months" (U. Kaspers et al., Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, Report Project No. 82S0124/98099, January 8, 2003). Fifty Wistar rats (Crl:Wist Han (GLX:BRL) BR) per sex per group received BAS 670 H, Batch Numbers N 17 and N26 (95.2% and 95.8% topramezone technical, respectively) in the diet at 0 (basal diet), 6, 60, 600, and 6000 ppm for 24 months. Group mean test article intake during the study was 0.4, 3.6, 36.4, and 381.5 mg/kg/day for males and 0.5, 4.7, 50.8, and 524.1 mg/kg/day for females at 6, 60, 600, and 6000 ppm, respectively. Treatment-related clinical observations during the study included an increased incidence of corneal opacity (of the right or left eye or of both eyes) in males and females at 60, 600, and 6000 ppm compared to controls. The incidence was 0, 1 (diagnosed as synechia and not treatment-related), 10, 34, and 41 for males and 0,1 (diagnosed as vitreous opacity, fundus not visible, not treatment-related), 12, 35, and 44 for females at 0, 6, 60, 600, and 6000 ppm, respectively. Additionally, an increased incidence of the anogenital region smeared with urine was noted for treated females compared to controls. The incidence was 5, 5, 8, 26, and 20 females at 0, 6, 60, 600, and 6000 ppm, respectively. Group mean bodyweight and bodyweight change were significantly reduced for males at 60 ppm and for males and females at 600 and 6000 ppm on several days during the study compared to controls. At necropsy, significant increases in group mean relative weights were recorded for liver, kidney, spleen, and adrenal glands in males at 60, 600, and 6000 ppm (and for spleens at 6 ppm) and for liver and kidneys in females at 600 and 6000 ppm compared to controls. Increases in cloudiness of the cornea at 60 ppm and higher were noted, the incidence was 0, 1, 10, 34, and 39 males and 0, 1, 8, 33, and 44 females at 0, 6, 60, 600, and 6000 ppm, respectively. The incidence of enlarged thyroid gland was increased for high dose males, and the number of thyroid masses was increased in treated groups for males and females, the incidence was 2, 7, 6, 9, and 12 for males and 0, 0, 4, 3, and 2 for females at 0, 6, 60, 600, and 6000 ppm, respectively. At histology, treatment-related neoplastic findings included a significant increase in thyroid follicular cell adenoma in high dose males and females compared to controls. Treatment-related non-neoplastic lesions included increases in diffuse thyroid follicular cell hypertrophy, in males at 60 ppm and in males and females at 600 and 6000 ppm, and in focal thyroid follicular cell hyperplasia, in females at 60 ppm and higher, compared to controls. Diffuse degeneration of the pancreas (mainly minimal to slight) was increased in males and females at 60, 600, and 6000 ppm compared to controls. The incidence was 0, 0, 1, 23, and 33 for males and 0, 0, 5, 10, and 19 for females at 0, 6, 60, 600, and 6000 ppm, respectively. Additionally, chronic keratitis (correlated to the corneal opacity seen at clinical observations and to the cloudiness of the cornea seen at necropsy) was noted in males and females at 60, 600, and 6000 ppm. The incidence (mainly slight to moderate) was 0, 0, 8, 32, and 41 for males and 0, 0, 7, 36, and 44 for females at 0, 6, 60, 600, and 6000 ppm, respectively. Chronic non-neoplastic NOEL (M & F) = 6 ppm (0.4 mg/kg/day for males and 0.5 mg/kg/day for females) based on thyroid, pancreas, and eye effects. **Possible adverse effect:** an increased incidence of thyroid follicular cell adenoma in males and females. Acceptable. (Green and Leung, 4/8/15).

Oncogenicity, mouse

**53271-0016 281700, "BAS 670 H – Carcinogenicity study in C57BL mice; Administration in the Diet for 18 months"; 832; C57BL/6 J Rj mice; Experimental Toxicology and Ecology, BASF Aktiengesellschaft, 67056 Ludwigshafen/Rhein, Germany. Document No. 2002/1014262 Project No.: 76C0124/9811212/6/2002; Mellert, W.; BAS 670 H, Lot No. N 17 and N 26, 95.2% or

95.8% pure, a beige solid. Groups of 50 male and 50 female C57BL mice were exposed to 0 (diet only), 80, 800, or 8000 ppm test substance in diet (mean actual test substance intake: 19, 194 and 1903 mg/kg/day for males of 80, 800, or 8000 ppm groups, respectively; 26, 256 and 2467 mg/kg/day for females of 80, 800, or 8000 ppm groups, respectively) for 18 months. Final mortality: 3/4, 3/4, 2/3 and 3/12 for 0, 80, 800 and 8000 ppm group males/females, respectively. No body weight, food consumption, hematology and organ weights changes that related to treatment were observed. Increased central liver hypertrophy was observed in 800ppm and 8000 ppm group males and 8000 ppm group females at terminal kill. **NOEL**: 80 ppm for males (19 mg/kg/day) and 800 ppm for females (256 mg/kg/day) due to histopathological findings. Not carcinogenic in mice. **Acceptable.** (Pan& Leung, 4/20/2015).

Gene Mutation

**53271-0026 281713, "Salmonella Typhimurium/Escherichia Coli Reverse Mutation Assay (Standard Plate Test and Preincubation Test) with BAS 670 H (=Reg.-Nr 375 080)" (G. Engelhardt and H.D. Hoffmann, Department of Toxicology of BASF Aktiengesellschaft, Ludwigshafen/Rhein, FRG, Report Project No. 40M0124/98210, October 29, 1999). Triplicate cultures of *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 *uvr*A were exposed to BAS 670 H (97.7% topramezone technical), in the presence and absence of rat liver S9 mix, at 0 (DMSO), 4, 20, 100, 500, 2500, or 5000 µg/plate for 48 to 72 hours (at 37°C) after plate incorporation. Trial one used direct plate incorporation, and trial two cultures were pre-incubated for 20 minutes at 37°C prior to plate incorporation. Cytotoxicity (reduced background lawn growth, reduced number of revertants per plate, and/or reduced titer) was noted at 2500 ppm with S9 mix in trial two (preincubation) and at 5000 ppm with and without S9 mix in trial one (direct plate incorporation). There was no increase in the number of revertants per plate in either trial compared to the vehicle controls. Positive controls were functional. No adverse effect. Acceptable. (Green and Leung, 5/18/15).

**53271-0024 281714, "Salmonella Typhimurium/Escherichia Coli Reverse Mutation Assay (Standard Plate Test and Preincubation Test) with BAS 670 H" (G. Engelhardt and E. Leibold, Experimental Toxicology and Ecology BASF Aktiengesellschaft, Ludwigshafen, Germany, Report Project No. 40M0124/984232, November 25, 2002). Triplicate cultures of *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 *uvr*A were exposed to BAS 670 H (99.3% topramezone technical), in the presence and absence of rat liver S9 mix, at 0 (DMSO), 4, 20, 100, 500, 2500, or 5000 µg/plate for 48 to 72 hours (at 37°C) after plate incorporation. Trial one used direct plate incorporation, and trial two cultures were pre-incubated for 20 minutes at 37°C prior to plate incorporation. Cytotoxicity (reduced number of revertants per plate and/or reduced titer) was noted depending on the strain and test conditions at 500 ug/plate and higher in both trials. There was no increase in the number of revertants per plate in either trial compared to vehicle controls. Positive controls were functional. No adverse effect. Acceptable (Green and Leung, 5/19/15).

**53271-0024 281715, "Salmonella Typhimurium/Escherichia Coli Reverse Mutation Assay (Standard Plate Test and Preincubation Test) with BAS 670 H" (G. Engelhardt and E. Leibold, Experimental Toxicology and Ecology BASF Aktiengesellschaft, Ludwigshafen, Germany, Report Project No. 40M0124/984234, December 9, 2002). Triplicate cultures of *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 *uvr*A were exposed to BAS 670 H (98.8% topramezone technical), in the presence and absence of rat liver S9 mix, at 0 (DMSO), 4, 20, 100, 500, 2500, or 5000 µg/plate for 48 to 72 hours (at 37°C) after plate incorporation. Trial one used direct plate incorporation, and trial two cultures

were pre-incubated for 20 minutes at 37°C prior to plate incorporation. Cytotoxicity (reduced background lawn growth, decreased numbers of revertants, and/or reduced titer) was indicated (depending on the strain and test conditions) at 2500 *u*g/plate and higher with direct plate incorporation and at 500 *u*g/plate and higher with preincubation. There was no increase in the number of revertants per plate in either trial compared to vehicle controls. Positive controls were functional. No adverse effect. Acceptable. (Green and Leung, 5/19/15).

****53271-0024 281716**, "Salmonella Typhimurium/Escherichia Coli Reverse Mutation Assay (Standard Plate Test and Preincubation Test) with BAS 670 H" (G. Engelhardt and E. Leibold, Experimental Toxicology and Ecology BASF Aktiengesellschaft, Ludwigshafen, Germany, Report Project No. 40M0124/984235, January 28, 2003). Triplicate cultures of *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 *uvr*A were exposed to BAS 670 H (95.8% topramezone technical), in the presence and absence of rat liver S9 mix, at 0 (DMSO), 4, 20, 100, 500, 2500, or 5000 μg/plate for 48 to 72 hours (at 37°C) after plate incorporation. Trial one used direct plate incorporation, and cultures for trial two were pre-incubated for 20 minutes at 37°C prior to plate incorporation. Subsequently, 2 additional trials were performed at 0 (DMSO), 3000, 4000, 5000, 6000, and 7000 μg/plate without activation using S. typhimurium strain TA98 only. The first additional trial used both direct plate incorporation and preincubation and the second trial used direct plating only. Cytotoxicity (reduced background lawn growth, decreased numbers of revertants, and/or reduced titer) was indicated with S9 mix at 2500 *u*g/plate and higher in trial 1 (direct plate incorporation) and at 500 *u*g/plate and higher in trial 2 (preincubation); and, in trial 3 using only strain TA98 with preincubation in the absence of activation, at 4000 *u*g/plate and higher. **There was a slight increase in the number of revertants per plate in S. typhimurium strain TA98 in the absence of S9 mix at 2500 *u*g/plate and higher under both direct plate incorporation and preincubation conditions.** Positive controls were functional. Acceptable. (Green and Leung, 5/20/15).

**53271-0024 281717, "In Vitro Gene Mutation Test with BAS 670 H in CHO Cells (HPRT Locus Assay)" (G. Engelhardt and H.D. Hoffmann, Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen, Germany, Report Project No. 50M0124/984183, November 10, 2000). CHO (substrain K1) Chinese hamster ovary cells were exposed in duplicate to BAS 670 H (95.8% topramezone technical), in the presence and absence of rat liver S9 mix, at 0 (DMSO), 78.13, 93.75, 156.25, 187.50, 312.50, 375, 625, 750, 1250, 1500, 2500, or 3000 *µ*g/ml for 4 hours at 37°C. At 3000 *µ*g/ml both with and without S9 mix, test material precipitation was observed (macroscopically). Precipitation was also noted microscopically at 1500 and 3000 *µ*g/ml in the absence of S9 mix. An increase in forward gene mutations was not indicated in the presence or absence of activation compared to solvent controls. The positive controls were functional. Acceptable. (Green and Leung, 5/21/15).

**53271-0025 281722 "Salmonella Typhimurium/Escherichia coli reverse mutation assay (Standard plate test and preincubation test) With Reg. No. 388 010", 842, Bacteria reverse mutation assay. Engelhardt, G., Experimental Toxicology and Ecology, BASF Aktiengesellschaft, 67056 Ludwigshafen/Rhein, Germany. 5/29/2001. Project No. 40M0362/984231. Reg. No. 388 010, light yellow powder, Batch N3, 99.3% pure, stored at room temperature. Test substance at up to 5000 ug/plate was tested in *Salmonella Typhimurium*, TA1537, TA 1535, TA98 and TA100 and E.coli WP2uvrA for potential mutagenicity with or without metabolic activation of rat liver S9-mix. Experiment 1, 2 and 3 used direct plate incorporation whereas in experiment 4, cultures were pre-incubated for 20 minutes at 37°C prior to plate incorporation. Strain specific positive control materials induced expected responses in

both assays with or without metabolic activation. Test substance showed negative responses over the dose range tested in all tester strains, with or without metabolic activation. The test substance is not mutagenic at the concentrations tested. Study acceptable. (Pan &Leung, 5/22/2015)

53271-0025, -0027; 281723, 285706 "Gene mutation assay (HPRT) in Chinese Hamster V79 cells in vitro with Reg. No. 388 010". Wollny, H-E., RCC Cytotest Cell Research GmbH, In den Leppsteinswiesen 19, D-64380 Roβdorf. 2/20/2001. Laboratory Project No. 50M0362/989168. Reg. No. 388 010 light yellow powder, Batch N3, 99.3% pure, stored at room temperature. Test substance up to 2800 ug/ml in DMSO was tested in for potential mutagenicity for 4 hours with or without metabolic activation of rat liver S9-mix. Treatment with test substance did not induce increased mutant colonies. The positive control materials induced increased mutant colonies as expected. The test substance is not mutagenic. The study plan was submitted in a separate report (Rec#: 285706). **Acceptable. (Pan & Leung, 7/16/2015)

Chromosome Effects

****53271-0024 281718**, "In Vitro Chromosome Aberration Assay with BAS 670 H in V79 Cells" (G. Engelhardt and H.D. Hoffmann, Department of Toxicology of BASF Aktiengesellschaft, Ludwigshafen/Rhein, FRG, Report Project No. 32M0124/984174, December 7, 1999). Chinese hamster V79 cells were exposed for 4 hours in duplicate to BAS 670 H (97.7% topramezone technical) at 0 (DMSO), 900, 1800, and 3600 *µ*g/ml in the presence and absence of rat liver S9 mix in the first assay and at 1800, 2700, and 3600 *µ*g/ml with rat liver S9 mix in the second assay. Cells were harvested 18 hours after the start of treatment in both assays. One hundred metaphases per duplicate culture (200 per concentration) were evaluated. Precipitation was noted (macroscopically) in the vehicle at 1800 and 3600 *u*g/ml and in the medium at 3600 *u*g/ml with and without metabolic activation in the first assay, and with activation in the vehicle at 2700 and 3600 *u*g/ml and in the medium at 1800 *u*g/ml and higher in the second assay. Mean relative mitotic indices at 3600 *u*g/ml were 68% (-S9) and 65% (+S9) of vehicle controls in the first assay and 110% of vehicle controls in the second assay. **Structural chromosome aberrations were significantly increased in metaphases treated at 3600 *u*g/ml in the first and second assays in the presence of rat liver S9 mix compared to vehicle controls.** Positive controls were functional. Acceptable. (Green and Leung, 5/26/15).

****53271-0024 281719**, "In Vitro Chromosome Aberration Assay with BAS 670 H in V79 Cells" (G. Engelhardt and E. Leibold, Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, Report Project No. 32M0124/984233, November 21, 2002). Chinese hamster V79 cells were exposed for 4 hours in duplicate to BAS 670 H (97.7% topramezone technical) at 0 (DMSO), 900, 1800, 2700, and 3600 *µ*g/ml in the presence and absence of rat liver S9 mix. Cells were harvested 18 hours after the start of treatment. Metaphases at 1800, 2700, and 3600 *u*g/ml were evaluated for chromosome aberrations. Structural chromosome damage was determined by evaluating 200 metaphases per concentration (100 metaphases from each duplicate culture). Precipitation was noted in the vehicle (macroscopically) at 900 ug/ml and above with and without metabolic activation and in the medium at 1800 *u*g/ml and higher with and without activation. Also, precipitation was microscopically visible in the medium at 3600 *u*g/ml without activation and at 1800 *u*g/ml and higher with activation. Mean relative mitotic indices at 3600 *u*g/ml were 121.0% (-S9) and 53.7% (+S9) of vehicle controls. **Structural chromosome aberrations were significantly increased in metaphases treated at 3600 *u*g/ml in the presence of rat liver S9 mix compared to vehicle controls.** Positive controls were functional. Acceptable. (Green and Leung, 5/27/15).

**53271-0024 281720, "Cytogenetic Study In Vivo with BAS 670 H in the Mouse Micronucleus Test After Two Intraperitoneal Administrations" (G. Engelhardt and H.D. Hoffmann, Department of Toxicology of BASF Aktiengesellschaft, Ludwigshafen/Rhein, FRG, Report Project No. 26M0124/984175, November 29, 1999). Five male NMRI mice per group received two intraperitoneal injections (IP) of BAS 670 H (97.7% topramezone technical) 24 twenty-four hours apart at 0 (aqueous 0.5% carboxymethylcellulose), 375, 750, and 1500 mg/kg followed by bone marrow sampling 24 hours after the second dose. All animals in all groups survived to sacrifice with clinical signs of treatment including piloerection, squatting posture, and/or poor general state lasting up to 4 hours after IP injection. An increase in micronucleated polychromatic erythrocytes was not indicated. Positive controls were functional. No adverse effect. Acceptable. (Green and Leung, 5/28/15).

53271- 0025 281724 "Cytogenetic study in Vivo with Reg. No. 388 010 in the Mouse Micronucleus test, single intraperitoneal administration". Engelhardt, G., Experimental Toxicology and Ecology, BASF Aktiengesellschaft, 67056 Ludwigshafen/Rhein, Germany. 5/14/2001. Laboratory Project No. 26M0362/984230. Reg. No. 388 010, light yellow powder, Batch N3, 99.3% pure, stored at room temperature. Six groups of five male NMRI mice received 0 (vehicle control), 200, 400 and 800 mg/kg of test substance and 2 positive control materials by a single intraperitoneal administration for 24 hour sacrifice interval. Two additional groups of five male NMRI mice received 0 (vehicle control) and 800 mg/kg of test substance by a single intraperitoneal administration for 48 hour sacrifice interval. There were no clinical signs of toxicity for all treatment group animals. Bone marrow slides were prepared for each animal and the slides were stained, evaluated for micronuclei in polychromatic and normochromatic erythrocytes. Positive control materials induced increases of polychromatic erythrocytes containing small and large micronuclei. The test substance did not cause significant increase in micronuclei from polychromatic and normochromatic erythrocytes compared with solvent control under conditions tested. **Study acceptable (Pan &Leung, 5/29/2015).

DNA Damage

**53271-0024 281721, "In Vitro Unscheduled DNA Systesis (sic) (UDS) Assay with BAS 670 H in Primary Rat Hepatocytes" (G. Engelhardt and H.D. Hoffmann, Department of Toxicology of BASF Aktiengesellschaft, Ludwigshafen/Rhein, FRG, Report Project No. 81M0124/984184, October 12, 1999). Primary rat hepatocytes derived from male Wistar rat (Chbb:THOM;SPF) livers (400,000 viable cells were seeded per 1.9 cm^2 well with 6 wells per test group) were exposed to BAS 670 H (97.7% topramezone technical) at 0 (untreated), 0 (DMSO), 10, 50, 100, 500, 1000, 2500, 3750, and 5000 µg/ml in Experiment 1 and at 0 (untreated), 0 (DMSO), 78.125, 156.25, 312.5, 625, 1250, and 2500 µg/ml in experiment 2 for 18 to 20 hours with ^{3}H-thymidine.100 cells per test group (using 2 or 3 slides) were analyzed. There was no increase in net nuclear grain counts. No adverse effect. Acceptable. (Green and Leung, 5/29/15).

REPRODUCTIVE TOXICITY, RAT

**53271-0022 281711, "BAS 670 H – Two-generation reproduction toxicity study in Wistar rats; Continuous dietary administration"; 834; Wistar rats; Experimental Toxicology and Ecology, BASF Aktiengesellschaft, 67056 Ludwigshafen/Rhein, Germany, Mellert, W.,

Laboratory Project ID: 70R0124/98136, BASF Registration Document # 2003/1006260, 2/25/2003; BAS 670H, Batch No. N26, 95.8% pure, a beige crystalline solid was administered to 25 rats (F0 parents)/sex/group at 0, 4, 40, 400, or 4000 ppm by diet once daily. [Mean test substance intake for F0 males: 0.3, 3.5, 35.0 and 355.3 mg/kg for 4, 40, 400, and 4000 ppm groups, respectively; 0.4, 4.1, 41.7 and 418.0 mg/kg for females in 4, 40, 400, and 4000 ppm groups, respectively.] At least 75 days after the beginning of administration, F0 animals were mated within each dosing group to produce F1 animals. [Mean test substance intake for F0 females in gestation period: 0.4, 3.6, 36.5 and 372.9 mg/kg for females in 4, 40, 400, and 4000 ppm groups, respectively; for F0 females in lactation period: 0.6, 6.2, 60.8 and 586.8 mg/kg for females in 4, 40, 400, and 4000 ppm groups, respectively.] Groups of 25/sex/group F1 pups were selected and were given the test diets at 0, 4, 40, 400, or 4000 ppm. [Mean test substance intake for F1 males: 0.5, 4.8, 49.3 and 498.2 mg/kg for 4, 40, 400, and 4000 ppm groups, respectively; 0.5, 5.0, 52.1 and 525.7 mg/kg for F1 females in 4, 40, 400, and 4000 ppm groups, respectively.] Breeding program was repeated and F2 litter was produced. [Mean test substance intake for F1 females in gestation period: 0.4, 3.7, 37.8 and 387.0 mg/kg for females in 4, 40, 400, and 4000 ppm groups, respectively; for F1 females in lactation period: 0.6, 6.1, 54.4 and 541.1 mg/kg for females in 4, 40, 400, and 4000 ppm groups, respectively.] The test diets were given until the F2 pups were weaned and F1 adults were sacrificed. Decreased F1 pups bodyweight at day 21 and decreased body weight gain from day 14 to day 21 was observed in 400 and 4000 ppm group males and females. Increased dead fetuses in F0 generation 4000 ppm group and in F1 generation 400 and 4000 ppm groups were observed. Decreased F2 pups bodyweight and decreased body weight gain from days 0 to 21 was observed in 40, 400 and 4000 ppm group males and females. Decreased spleen weight in 40, 400 and 4000 ppm group F1 litter, and decreased relative spleen weight in all treated F2 litter groups were observed. Eye opacity was observed in 400 and 4000 ppm group F0 males and 40, 400 and 4000 ppm groups F0 females (except for gestation period), in 40, 400 and 4000 ppm group F1 males and in 400 and 4000 ppm group F1 females. Increased liver, kidney and thyroid weights in 40, 400 and 4000 ppm group F0 males, increased kidney weights in 40, 400 and 4000 ppm group F0 females, increased kidney weight and relative liver weight, decreased spleen absolute weight in 40, 400 and 4000 ppm group F1 males, increased relative kidney weight in 40, 400 and 4000 ppm group F1 females, and increased absolute thyroid weight in all treated F1 females were observed. Thyroid flaky colloid was observed in all treated F0 and F1 males, in 40, 400 and 4000 ppm group F0 and F1 females. Increase dead pups in F0 generation 4000 ppm group and in 400 and 4000 ppm groups of F1 generation were observed. Increased kidney pelvic dilation in 40, 400 and 4000 ppm group F1 males and females were observed. **Parental NOEL:** F0 generation**:** < 4 ppm (0.3 mg/kg/day) for males due to increased thyroid flaky colloid and 4 ppm for females (0.4 mg/kg/day) due to cornea opacity; F1 generation: < 4 ppm for males (0.5 mg/kg/day) and 4 ppm for females (0.5 mg/kg/day) due to increased thyroid flaky colloid; **Reproductive NOEL:** 400 ppm for F0 generation (35.0 and 41.7 mg/kg/day for males and females, respectively) and 40 ppm for F1 generation (4.8 and 5.0 mg/kg/day for males and females, respectively) due to increased dead pups; **Developmental NOEL:** 40 ppm for F1 pups (3.6 - 6.2 mg/kg/day, respectively), and 4 ppm for F2 (0.4-0.6 mg/kg/day) pups due to decreased pup weight. **ACCEPTABLE**. (Pan & Leung, 5/21/2015)

DEVELOPMENTAL TOXICITY

Rat

53271-0018 281704, "BAS 670 H – Prenatal development toxicity study in Wistar rats; Oral administration (Gavage)"; 833; Wistar rats; Experimental Toxicology and Ecology, BASF Aktiengesellschaft, 67056 Ludwigshafen/Rhein, Germany, Schneider, S., Laboratory Project ID: 30R0124/98120, BASF Registration Document # 2003/1006253, 2/27/2003; BAS 670H, Batch No. N26, 95.8% pure, a beige crystalline solid was administered to 25 pregnant rats/group at 0, 100, 300 or 1000 mg/kg in 0.5% methylcellulose once daily from day 6 to day 19 post coitum inclusive. The rats were observed for clinical signs, body weight, food and water consumption during the treatment period. On day 20 post coitum, all rats were killed by cervical dislocation, dissected and examined for macroscopic pathological changes in maternal organs. The ovaries and uteri were examined to determine: the number of corpora lutea, number and distribution of live young fetuses, fetal weight and gross abnormalities. No maternal mortality. No treatment related effects on clinical signs, maternal body weight, food consumption, necropsy and reproduction data. Increased percentage of fetuses per litter with skeletal variations, including delayed ossification of vertebral column, ribs and sternbrae, and decreased fetal bodyweights in all treated groups were observed. **Maternal NOEL = 1000 mg/kg/day due to no treatment related effects at HDT. **Developmental NOEL:** <100 mg/kg/day due to decreased fetal weights and skeletal variations in all treated groups. **ACCEPTABLE**. (Pan & Leung, 4/24/2015)

Rabbit

**53271-0019 281707, "A Definitive Oral Developmental Toxicity (Embryo-Fetal Toxicity/Teratogenicity) Study with BAS 670H in Rabbits" (J.F. Barnett, Argus Research Laboratories, Inc., Horsham, PA., Study No. 101-037, March 13, 2003). Twenty-five time-mated female Hra:(NZW)SPF rabbits per group received BAS 670H (95.8% topramezone technical) by oral gavage at 0 (0.5% aqueous carboxymethylcellulose), 0.5, 5, 50, and 450 mg/kg/day on gestation days 6 through 28. Twenty-three, 24, 24, 21, and 23 live litters with mean live litter sizes of 8.4, 8.7, 7.3, 9.1, and 7.5 resulted at 0, 0.5, 5, 50, and 450 mg/kg/day, respectively. Treatment-related maternal clinical signs included a significant increase in the number of does with scant feces, and an increase (ns) in the number of does with tan discoloration of the feces at 450 mg/kg/day compared to controls. Group mean maternal bodyweight gain was significantly reduced at 450 mg/kg/day for gestation days 6 to 29 and 20 to 24 compared to controls. Gravid uterine weights (g) were significantly reduced at the high dose level compared to controls. At 450 mg/kg/day, group mean maternal absolute food consumption (g/day) was significantly reduced for gestation days 6 to 10 compared to controls, and group mean maternal absolute and relative (g/kg/day) food consumption was reduced (ns) for gestation days 6 to 29. Group mean fetal bodyweights were significantly reduced at 450 mg/kg/day compared to controls. No treatment-related fetal gross external, soft tissue, or skeletal malformations were noted at 0.5, 5, 50, or 450 mg/kg/day compared to controls. Maternal NOEL = 50 mg/kg/day based on clinical signs, bodyweight gain, and food consumption. Developmental NOEL = 50 mg/kg/day based on reduced fetal bodyweights. Teratogenicity was not indicated. Acceptable. (Green and Leung, 4/15/15).

53271-0020 281708, "BAS 670 H – Prenatal Developmental Toxicity Study in New Zealand White Rabbits, Oral Administration (Gavage)" (S. Schneider et al., Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen, Germany, Report Project No. 40R0124/98170, March 13, 2003). Twenty-five female time-mated New Zealand White rabbits (Crl:KBL(NZW)) per group received BAS 670 H (98.7% topramezone technical) by oral gavage at 0 (0.5% aqueous carboxymethylcellulose), 5, 50, and 500 mg/kg/day on gestation days 6 through 28. Twenty-one, 23, 22, and 19 live litters with mean live litter sizes of 8.7, 9.1, 8.7, and 7.7 resulted at 0, 5, 50, and 500 mg/kg/day, respectively. The group mean incidence of post-implantation loss was significantly increased at 500 mg/kg/day compared to controls (19.2% vs 4.5%). Group mean maternal serum tyrosine levels were significantly increased at 5, 50, and 500 mg/kg/day compared to controls and appeared to become saturated at the mid and high dose levels. A significant increase in fetal external malformations was noted at 500 mg/kg/day (1 fetus from each of 3 litters had gastroschisis or thoracochisis). Additionally, the group mean incidence of fetal soft tissue malformations was significantly increased at the mid and high dose levels compared to controls (the unilateral absence of kidney and ureter was noted in 2, 1, 1, and 1 fetuses/litter at the mid dose and 2, 4, 1, and 1 fetuses/litter at the high dose level) compared to controls (0 incidence)). The overall group mean fetuses/litter incidence of all soft tissue malformations was 0.8%, 2.2%, 5.2%, 14.5% at 0, 5, 50, and 500 mg/kg/day, respectively with statistical significance at the high dose level. Maternal NOEL < 5 mg/kg/day based on serum tyrosine levels. Developmental NOEL = 5 mg/kg/day based on fetal soft tissue malformations. **Possible adverse effects**: fetal external malformations (gastro- or thoracochisis) and fetal soft tissue malformations (unilateral absence of kidney and ureter). Unacceptable and possibly upgradeable with submission of fetal skeletal evaluation procedures and results. (Green and Leung, 4/20/15).

****53271-0020 281709**, "BAS 670 H – Prenatal Developmental Toxicity Study in New Zealand White Rabbits, Oral Administration (Gavage)" (S. Schneider et al., Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen, Germany, Report Project No. 40R0124/98148, February 27, 2003). Twenty-five time-mated female New Zealand White rabbits (Crl:KBL(NZW)) per group received 0 (0.5% aqueous carboxymethylcellulose), and BAS 670 H Batch Numbers N17 and N26 (95.2%and 95.8% topramezone technical) at 1.5 and 5 mg/kg/day each by oral gavage on gestation days 6 through 28. Maternal serum tyrosine levels were significantly increased at 1.5 and 5 mg/kg/day with both BAS 670 H batches N17 and N26. Group mean values were increased by 177.6% and 563.23% over control concentrations with batch N17 and 243.36% and 504.41% over control concentrations with batch N26 at 1.5 and 5 mg/kg/day, respectively. Group mean fetal bodyweight was significantly reduced for both sexes combined and for males at 5 mg/kg/day with BAS No. 670 H batch No. N26 compared to controls. Fetal soft tissue malformations were noted at 1.5 and 5 mg/kg/day in litters from does treated with both BAS 670 H batch No. N17 and N26. The fetal incidence of unilaterally absent kidney and ureter was 3 fetuses (1 from 1 litter and 2 from another) at 1.5 mg/kg/day; 2 fetuses from 1 litter at 5 mg/kg/day with batch No. N17; and 1 fetus each at 1.5 and 5 mg/kg/day, respectively with batch No. N26 compared to controls (0 incidence). Treatment-related skeletal malformations were not indicated. A significant non-dose dependent increase in the fetuses/litter incidence of the skeletal variations supernumerary thoracic vertebrae and supernumerary (13th) ribs was noted at all treated levels with both batches. Maternal NOEL < 1.5 mg/kg/day based on maternal tyrosine levels. Developmental NOEL < 1.5 mg/kg/day based on increased fetal soft tissue malformations and fetal skeletal variations. **Possible adverse effects:** fetal soft tissue malformations (unilateral absence of kidney and ureter) was indicated. Acceptable. (Green and Leung, 4/22/15).

53271-0021 281710, "BAS 670 H – Prenatal Developmental Toxicity Study in New Zealand White Rabbits, Oral Administration (Gavage)" (S. Schneider and B.V. Ravenzwaay, Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen, Germany, Report Project No. 40R0124/98150, February 28, 2003). Twenty-five time-mated female New Zealand White rabbits (Crl:KBL(NZW)) per group received BAS 670 H (Batch. N33, 98.8% topramezone technical) at 0 (0.5% aqueous carboxymethylcellulose), 1.5, and 5 mg/kg/day, and Batches N17/CFR1, N17/CFR2, and N17/CFR3 (purity not provided) at 1.5, 1.5, and 0.5 mg/kg/day, respectively by oral gavage on gestation days 6 through 28. No treatment-related effects were noted for group mean values for maternal mortality, clinical signs, food consumption, bodyweight, conception rate, uterine weight, or necropsy results, and number of corpora lutea, implantation sites, pre- and post-implantation losses, number of resorptions, viable fetuses, placental weights, or fetal bodyweights in any of the treated groups with any of the 4 BAS 670 H batch numbers compared to controls. The group mean rate of fetuses per litter with skeletal variations was significantly increased in fetuses from does that received 1.5 and 5 mg/kg/day of Bas 670 H batch N33 and 1.5 mg/kg/day of batch N17 CFR 1 compared to controls based on an increase in supernumerary thoracic vertebrae along with supernumerary (13th) ribs. Additionally, significantly increased incidences of incompletely ossified sternebrae were noted with BAS 670 H batch numbers N17/CFR 1 (1.5 mg/kg/day) and N17/CFR3 (0.5 mg/kg/day) compared to controls. No treatment-related increases in the incidence of fetal external, soft tissue, or skeletal malformations were noted for any treated group with any of the 4 BAS 670 H batch numbers compared to controls. Maternal NOEL = 5.0 mg/kg/day (no effect at the HDT). Developmental NOEL < 0.5 mg/kg/day (based on delayed ossification of sternebrae). Teratogenicity was not indicated. Unacceptable, possibly upgradeable with submission of the purity of the chromatographic fractions BAS 670 H N17/ CFR1, N17/CFR2, and N17/CFR3. (Green and Leung, 4/27/15).

Mouse

**53271-0019 281705, 281706, "Oral (Gavage) Developmental Toxicity Study of BAS 670H in Mice" (J.F. Barnett, Argus Research Laboratories, Inc., Horsham, PA., Study No. 101-041, March 11, 2003). Twenty-five sperm positive female Crl:CD-1®(ICR)BR mice per group received BAS 670H (99.7% topramezone technical) by oral gavage at 0 (0.5% aqueous sodium carboxymethylcellulose), 30, 200, and 1000 mg/kg/day on gestation days 6 through 17. Group mean maternal bodyweight change was significantly reduced at the high dose level for gestation days 6 to 9. Group mean maternal serum alanine aminotransferase activity and calcium values were significantly increased at 1000 mg/kg/day compared to controls. Group mean maternal serum tyrosine levels were significantly increased at 30, 200, and 1000 mg/kg/day compared to controls. Values were 2 to 3 times the control values at 30 mg/kg/day and 6 to 10 times the control values at 200 and 1000 mg/kg/day. Group mean maternal relative liver weights were significantly increased at 1000 kg/mg/day compared to controls. There were no treatment-related effects on the pregnancy rate, pre- and post-implantation loss, early or late resorptions, percentage of male and female fetuses, fetal bodyweights, fetal external observations, fetal visceral examinations, or fetal skeletal evaluations at 30, 200, or 1000 mg/kg/day compared to controls. Record 281705 is a mouse oral (gavage) dose-ranging developmental toxicity study. Maternal NOEL = 30 mg/kg/day based on maternal tyrosine levels. Developmental NOEL = 1000 mg/kg/day. Teratogenicity was not indicated. Acceptable. (Green and Leung, 4/13/15).

53271-0019 281705, "Oral (Gavage) Dosage-Range Developmental Toxicity Study of BAS 670H in Mice" (J.F. Barnett, Argus Research Laboratories, Inc., Horsham, PA., Study No. 101-041P, March 5, 203). Nine sperm-positive female Crl:CD-1®(ICR)BR mice per group received

BAS 670H by oral gavage at 0 (0.5% carboxymethylcellulose), 30, 100, 300, and 1000 mg/kg/day on gestation days 6 through 17. All mice survived to scheduled sacrifice with no treatment-related clinical signs. Nine, 9, 8, 9, and 7 females at 0, 30, 100, 300, and 1000 mg/kg/day, respectively were pregnant. There were no treatment-related effects on maternal clinical signs, bodyweight, bodyweight gain, or organ weights. Maternal serum chemistry and tyrosine level determinations were made from 3 females each, and fetal tyrosine levels were determined from pooled samples (sexes separate) of all fetuses per litter on day 18. Non dose-dependent increases in maternal group mean serum glucose, alanine aminotransferase activity, aspartate aminotransferase activity, and alkaline phosphatase activity were noted at the high dose level compared to controls. Maternal tyrosine levels increased with increasing dose compared to controls. Significant increases in fetal tyrosine levels were noted for males and females at 30, 100, 300, and 1000 mg/kg/day compared to controls. Supplemental data. (Green, 4/10/15). No worksheet.

NEUROTOXICITY

Rat Acute Oral Neurotoxicity Study

**53271-0007 281687, "BAS 670 H, Acute Neurotoxicity Study in Wistar Rats, Single Administration by Gavage" (U. Kaspers et al, Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, Report Project No. 20S0124/98127, September 6, 2002). Ten Wistar rats (CrlGlxBrlHan:WI) per sex per group received a single oral gavage dose of BAS 670 H (95.8% topramezone technical) at 0 (0.5% carboxymethylcellulose (CMC) in doubly distilled water), 125, 500, and 2000 mg/kg followed by a 14-day observation period. There were no treatment-related effects on mortality, clinical signs, bodyweight, functional observational battery (FOB) evaluations, motor activity assessment, necropsy findings, or histopathology results at 125, 500, or 2000 mg/kg compared to controls. Systemic NOEL (M & F) = 2000 mg/kg. Neurotoxicity was not indicated. Acceptable. (Green, 3/12/15).

Rat 90-day (Dietary) Neurotoxicity Study

**53271-0008 281688, "BAS 670H – Subchronic toxicity and Neurotoxicity Study in Wistar Rats; Administration in the Diet for 3 months"; 827; Rat; Experimental Toxicology and Ecology, BASF Aktiengesellschaft, 67056 Ludwigshafen/Rhein, Germany, Kaspers, U., Laboratory Project ID: 50S0124/98 142, BASF Registration Document # 2002/1014197, 12/9/2002; BAS 670H, Batch No. N 26, 95.8% pure, a beige solid was administered to 15 rats/sex by diet at 0, 60, 600, or 6000 ppm [mean test substance intake: 0, 4.2, 43.8, and 432.9 mg/kg/day for males; 0, 5.0, 50.9 and 510.1 mg/kg/day for females, respectively] for 3 months. Animals were observed for general condition, detailed clinical examinations, functional observational battery (FOB), motor activity tests, neurohistology and neurohistopathology. No mortality. No test substance treatment related changes in body weight, bodyweight gains, food consumption, functional observational battery (FOB) and motor activity tests in both males and females were observed. Increased ophthalmological findings in Groups 2 and 3 males and females at the end of the treatment period, increased incidence of ketone in the urine of all treated animals, increased transitional epithelial cells and casts in all treated group males, increased relative liver and kidney weights in all, and microscopic findings including changes in flaky colloid in thyroid and diffuse degeneration in pancreas in all treated groups, chronic keratitis in eyes in groups 2 and 3,

central hypertrophy in liver of high dose group males were observed. Positive control studies conducted by the testing facility demonstrated the ability of the observational methods to detect major neurotoxic endpoints and the sensitivity and reliability of the activity-measuring device and testing procedures. **NOEL (No Observed Effect Level) for neurotoxicity**: 6000 ppm (432.9 and 510.1 mg/kg/day for male rats and female rats, respectively). **NOEL (No Observed Effect Level)** for systematic toxicity (M/F): < 60 ppm (4.2 mg/kg/day for males, 5.0 mg/kg/day for females, respectively) due to urinalysis, organ weights and microscopic findings**.** **Acceptable**. (Pan& Leung, 4/2/2015).

Rat Developmental Neurotoxicity Study

**53271-0023 281712, "BAS 670 H – Developmental Neurotoxicity Study in Wistar Rats, Administration in the Diet" (W. Kaufmann et al., Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen, Germany, Report Project No. 67R0124/98140, March 11, 2003). Thirty eight (control) to 39 (treated group) time-mated female Wistar rats (CrlGlxBrlHan:WI (former name: CRL:WI(GLX/BRL/HAN) IGS BR)) received BAS 670 H Batch number N26 (95.8% topramezone technical) in the diet at 0 (basal diet), 8, 80, and 800 mg/kg/day from gestation day 6 through lactation day 21. All dams survived to the end of the study. Corneal opacity was noted in 0, 4, 22, and 12 dams at 0, 8, 80, and 800 mg/kg/day, respectively during lactation. The finding first appeared at lactation day 7 at the mid and high dose level and at day 13 in low dose dams. Group mean food consumption was significantly reduced at the mid and high dose levels on gestation days 6 to 13 and on lactation days 1 to 14 compared to controls. Group mean maternal bodyweight was significantly reduced for high dose dams on gestation day 13 and on lactation day 14, and significant reductions in group mean bodyweight gain were noted for mid and high dose dams on gestation days 6 to 13 compared to controls. Group mean pup weights were significantly reduced at the mid and high dose levels on lactation days 4 to 21 compared to controls and for low dose males (subset IV) for post-weaning weeks 2 and 4. The time to preputial separation was significantly increased for male pups at 80 and 800 mg/kg/day compared to controls, and corneal opacity was observed in 1 pup per sex at the mid dose and 3 pups per sex at the high dose level. In the auditory startle test, significantly decreased values of mean maximum amplitude were noted in male and female pups at the low, mid, and high dose levels compared to controls on post-partum (p.p.) day 24. Pup group mean absolute brain weights were significantly reduced at the low dose (for males on p.p. day 62 and for females on p.p. day 22), and at the mid and high dose levels for both sexes on p.p. days 22 and 62 compared to controls. However, pup group mean relative brain weights were increased at the low, mid, and high dose levels for males (p.p. days 22 and 62) and females (p.p. day 22) compared to controls with statistical significance in both sexes at the mid and high dose levels on p.p. day 22 (an indication that absolute brain weight values probably correlate to pup weight reductions). Significant reductions in pup brain width were noted at the low dose in females and in brain length and width at the mid and high dose levels in both sexes at p.p. day 22 compared to controls. Additionally, group mean pup brain lengths were significantly reduced at the low, mid, and high dose levels in both sexes at p.p. day 62 compared to controls. Significantly smaller parietal cortices were noted at the low dose in both sexes at p.p. day 62. Significantly smaller frontal and parietal cortices were noted at the mid dose (females at p.p. day 22 and 62 and males (parietal cortex) at p.p. day 62) and high dose (males at p.p.day 62 and females at p.p. day 22 and 62) compared to controls. Significantly smaller hippocampi were noted at the low, mid, and high dose levels in both sexes at p.p. days 22 and 62 compared to controls. As with the brain weights, these morphometric brain changes correlate to the reduced pup weights. Histology results included bi- or unilateral keratitis of the eye (minimal (grade 1) to moderate (grade 3) with severity increasing with dose

level) in 1 male at the low dose, 3 pups per sex at the mid dose, and all pups at the high dose level on p.p. day 22 compared to controls (0 incidence) (the finding was not present in the p.p. day 62 sacrifice microscopy results, however, 1 pup per sex at the high dose level had cloudiness of the cornea). There was no treatment-related effect on the total number of pups delivered, the mean or number of pups per dam, the total number of liveborn pups, pup viability or mortality, sex distribution/sex ratios of live pups, pup motor activity, or pup water maze testing results at the low, mid, and high dose levels compared to controls. Maternal NOEL < 8 mg/kg/day based on corneal opacity. Developmental NOEL < 8 mg/kg/day based on corneal keratitis and reduced pup weights. Developmental Neurotoxicity NOAEL = 800 mg/kg/day. No adverse effect. Acceptable. (Green and Leung, 4/30/15).

Delayed neurotoxicity, hen

No required at this time.

IMMUNOTOXICITY

Mouse 4-Week Dietary Immunotoxicity Study

**53271-0026 281728, "BAS 670 H (Topramezone), Immunotoxicity Study in Female C57BL/6 J Rj Mice, Administration via the Diet for 4 Weeks" (R. Buesen et al., Experimental Toxicology and Ecology, BASF SE, Ludwigshafen, Germany, Report Project No. 43C0124/98S001, December 1, 2011). Eight female C57BL/6 J Rj mice per group received BAS 670 H (99.2% topramezone) in the diet at 0 (basal diet), 500, 1500, and 5000 ppm for 4 weeks. Group mean test article intake was 168, 523, and 1615 mg/kg/day at 500, 1500, and 5000 ppm, respectively. All animals survived to scheduled sacrifice. No treatment-related effects were noted for clinical signs, food or water consumption, bodyweight, or spleen and thymus weights of animals at 500, 1500, and 5000 ppm compared to vehicle controls. Enzyme linked immunosorbent assay (ELISA) results showed no treatment-related reductions in SRBC IgM titers for animals at 500, 1500, and 5000 ppm compared to vehicle controls. The positive control group was functional. Systemic NOEL for female mice = 5000 ppm (1615 mg/kg/day). Immunotoxicity NOEL for female mice > 5000 ppm. Acceptable. (Green, 5/15/15).

ENDOCRINE DISRUPTOR STUDIES

No studies on file.

SUPPLEMENTAL STUDIES

53271-0015 281697, "BAS 670 H – Determination of serum tyrosine in male Wistar Rats and in male C57BL-mice; Administration in the Diet for 2 weeks"; supp; Rat and mouse; Experimental Toxicology and Ecology, BASF Aktiengesellschaft, 67056 Ludwigshafen/Rhein, Germany, Mellert, W., Laboratory Project ID: 99S0124/98129, BASF Registration Document # 2002/1011884, 10/14/2002; BAS 670H, Batch No. N 26, 95.8% pure, a beige solid was administered to 5 male rats and 15 male mice by diet at 0, 6, 60, or 600 ppm [mean test substance intake: 0.6, 5.9 and 62.0 mg/kg/day for rats; 1.7, 16.6 and 150.3 mg/kg/day for mice of

6, 60, and 600 ppm groups, respectively] for 2 weeks. Animals were observed for clinical signs and mortality, body weight and food consumption. Serum tyrosine level was determined on days 1, 7, 14 days of study from 5 rats or 5 mice per group. No mortality. No test substance treatment related changes in body weight and food consumption were observed. Increased tyrosine level in all treated rats and mice was observed from day 1 to 14, with more pronounced increase in rats. **NOEL (No Observed Effect Level)**: < 6 ppm (0.6 and 1.7 mg/kg/day for male rats male mice, respectively). **Supplemental**. (Pan& Leung, 4/6/2015).

53271-0015 281698, "BAS 670 H – Tyrosine-determination in male Wistar Rats; Administration in the Diet for 2 weeks"; supp; Rat; Experimental Toxicology and Ecology, BASF Aktiengesellschaft, 67056 Ludwigshafen/Rhein, Germany, Kaspers, U., Laboratory Project ID: 99S0124/98165, BASF Registration Document # 2003/1005347, 2/6/2003; BAS 670H, Batch No. 30786/22, 99.3% pure, a beige solid was administered to 10 male rats by diet at 0, 1, 2, 3, 4 or 5 ppm [mean test substance intake: 0.1, 0.2, 0.3, 0.4 and 0.5 mg/kg/day for rats of 1, 2, 3, 4 and 5 ppm groups, respectively] for 2 weeks. Animals were observed for clinical signs and mortality, body weight and food consumption. Serum tyrosine level and tyrosine aminotransferase activities in the liver were determined on day 14 of study. No mortality. No test substance treatment related changes in body weight, food consumption, clinical signs or gross lesions were observed. Increased serum tyrosine level and tyrosine aminotransferase activities in the liver in all treated rats were observed at day 14. **NOEL (No Observed Effect Level)** for serum tyrosine level and tyrosine aminotransferase activities in the liver: < 1 ppm (0.1 mg/kg/day) for male rats treated for 2 weeks in the diet. **Supplemental**. (Pan& Leung, 4/7/2015).

53271-0015 281699, "BAS 670 H – Tyrosine-determination in male C57BL mice; Administration in the Diet for 2 weeks"; supp; C57BL mice; Experimental Toxicology and Ecology, BASF Aktiengesellschaft, 67056 Ludwigshafen/Rhein, Germany, Kaspers, U., Laboratory Project ID: 99S0124/98164, BASF Registration Document # 2003/1005346, 2/6/2003; BAS 670H, Batch No. 30786/22, 99.3% pure, a beige solid was administered to 10 male mice by diet at 0, 1, 2, 3, 4 or 5 ppm [mean test substance intake: 0.2, 0.5, 0.7, 0.9 and 1.2 mg/kg/day for mice of 1, 2, 3, 4 and 5 ppm groups, respectively] for 2 weeks. Animals were observed for clinical signs and mortality, body weight and food consumption. Serum tyrosine level and tyrosine aminotransferase activities in the liver were determined on day 14 of study. No mortality. No test substance treatment related changes in body weight, food consumption, clinical signs or gross lesions were observed. Increased serum tyrosine level and tyrosine aminotransferase activities in the liver in all treated mice were observed at day 14. **NOEL (No Observed Effect Level)** for serum tyrosine level and tyrosine aminotransferase activities in the liver: < 1 ppm (0.2 mg/kg/day) for male mice treated for 2 weeks in the diet. **Supplemental**. (Pan& Leung, 4/7/2015).

53271-0018 281702, "BAS 670 H – Thyroid hormone study in Wistar rats; Administration in the Diet for 4 weeks and recovery periods up to 13 weeks"; supp; Wistar rats; Experimental Toxicology and Ecology, BASF Aktiengesellschaft, 67056 Ludwigshafen/Rhein, Germany, Mellert, W., Laboratory Project ID: 37C0124/98159, BASF Registration Document # 2002/1014188, 12/6/2002; BAS 670H, Batch No. N26, 95.8% pure, a grey crystalline solid was administered to 5/sex/group rats by diet at 0, 6, 60, 600, or 6000 ppm for 4 weeks. Additional

groups were treated with the same concentrations for 4 weeks (groups 00-04), followed with a 4 week (groups 10-14) or a 13 week(groups 20-24) recovery periods. [Mean test substance intake: 0.4, 3.6, 35.4, and 360.7 mg/kg/day for male rats of 6, 60, 600, and 6000 ppm groups, 0.4, 4.3, 43.0 and 439.5 mg/kg/day for female rats of 6, 60, 600, and 6000 ppm groups respectively]. Animals were observed for clinical signs and mortality, body weight and food consumption. Serum hormone (including total triiodothyronine(T3), total thyroxine (T4), and thyroid stimulating hormone (TSH)) levels were determined on days 14, 28 and at the end of 4 week and 13 week recovery periods. No mortality. No test substance treatment related changes in body weight, food consumption, clinical signs or gross lesions were observed. Decreased serum total thyroxine (T4) level was observed on days 14 and 28 in 60, 600 and 6000 ppm group males. Increased thyroid stimulating hormone (TSH) level was seen in main study 600 and 6000 ppm group males after 28 days of treatment. These effects are reversed after 4 week or 13 week recovery periods. No treatment related effects were seen in female rats. Increased absolute and relative thyroid weights were observed in 60, 600 and 6000 ppm group males after 13 week recovery period. Increased severity of altered (flaky) colloid was seen in high dose males at the end of 4 week treatment, and at the end of 4 week recovery period. **NOEL (No Observed Effect Level)** for thyroid hormones for males: 6 ppm (0.4 mg/kg/day) due to decreased total thyroxine (T4) level. **Supplemental**. (Pan& Leung, 4/23/2015).

53271-0018 281703, "BAS 670 H – Hepatic enzyme induction study in Wistar rats; Administration in the Diet for 4 weeks"; supp; Wistar rats; Experimental Toxicology and Ecology, BASF Aktiengesellschaft, 67056 Ludwigshafen/Rhein, Germany, Mellert, W., Laboratory Project ID: 99C0124/98161, BASF Registration Document # 2002/1013897, 11/19/2002; BAS 670H, Batch No. N26, 95.8% pure, a beige crystalline solid was administered to 5/sex/group rats by diet at 0 or 6000 ppm for 4 weeks. [Mean test substance intake: 557.9 mg/kg/day and 593.6 mg/kg/day for male and female rats of 6000 ppm groups, respectively]. Animals were observed for clinical signs and mortality, body weight and food consumption. Liver enzymes including p-Nitrophenol-glucuronyltransferase (pNP-GT), 4-Methylumbelliferone-glucuronyltransferase (MUF-GT) and 4-Hydroxybiphenyl-glucuronyltransferase (HOBI-GT) were evaluated at the end of the 4 week exposure. No mortality. No test substance treatment related changes in body weight, food consumption, or clinical signs were observed. Slightly increased 4-Methylumbelliferone-glucuronyltransferase (MUF-GT) (1.7-fold in treated males, 1.28-fold in treated females) and liver weights in males were observed. **NOEL (No Observed Effect Level)** for liver enzyme induction for males: < 6000 ppm (557.9 mg/kg/day and 593.6 mg/kg/day for male and female rats, respectively) due to slightly increased MUF-GT activity in male and female rats and liver weights in male rats. **Supplemental**. (Pan& Leung, 4/23/2015).