CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
Metrafenone

Chemical Code # 5990, Tolerance # 53072

3 November 2009

I. DATA GAP STATUS

Combined toxicity, rat:	No data gap, possible adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, possible adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

All record numbers through 242816 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.

File name: T091103, prepared by H. Green

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

COMBINED, RAT

****53072-0029, 0030, 0031, 0040, 0041, 0032 241638, 241639, 241640, 241641, 241642, 241643, 241659, 241660, and 241644,** "A 24-Month Dietary Toxicity and Oncogenicity Study with BAS 560F in Rats", (C. M. Kelly, Huntingdon Life Sciences, East Millstone, NJ, Laboratory Project ID. 98-2606, 1 April 2002). 65 albino (outbred) VAF/Plus® CD® (Sprague-Dawley derived) Crl:CD® (SD)IGS BR rats per sex per group received BAS 560F (95.86% metrafenone) in the diet at 0 (basal diet), 500, 5000, and 20,000 ppm for 24 months. Additional groups of 10 animals per sex per group were necropsied after 12 months of treatment. Beginning on the first day of treatment week 69, the dietary level for high dose females was decreased to 10,000 ppm as a result of decreased bodyweight and liver histology.

Group test article intake values were 24.9, 260.0, and 1068.5 mg/kg/day for males and 30.4, 320.2, and 1418.6 mg/kg/day for females through 104 weeks at 500, 5000, and 20,000 ppm, respectively (this represents the value at the high dose for females through the end of week 68, after which, the dose level was lowered to 10,000 ppm (due to bodyweight loss) and the resulting intake value at the high dose level was 592.8 mg/kg/day for weeks 72 through 104 for females).

At 5000 and 20,000 ppm, significant decreases in group mean female bodyweight (-12% and -26%, respectively) and bodyweight gain (-21% and -42%, respectively) were noted compared to controls through 52 weeks. Male bodyweight was reduced at the high dose level (with intermittent statistical significance) through 104 weeks. After 24 months of treatment, bodyweight gains were significantly reduced at the mid (-26%) and high dose levels (-42%) in females and at the high dose level in males (-14%, ns) compared to controls. Group mean food consumption values (g/kg/day) for males and females at the mid and high dose levels were generally significantly increased through treatment week 104. Time-dependent decreases (marginal to moderate) in group mean hemoglobin, hematocrit, erythrocyte, mean corpuscular volume, mean corpuscular hemoglobin, and mean hemoglobin concentration values and increases in platelet counts were noted for females at 20,000 ppm compared to controls after 3, 6, and 12 months of treatment. Mild to moderate decreases in group mean hemoglobin, hematocrit, and erythrocyte values were noted for mid and high dose females compared to controls after 18 months of treatment. 24 month values were generally comparable to controls. Male values for the above parameters were generally comparable to controls during the 24 month treatment period. Mild prolongation of group mean activated partial thromboplastin time was noted for males and females at 5000 and 20,000 ppm after 3 months and for males, at the high dose, after 6 and 12 months compared to controls (24 month values were comparable to controls). Group mean prothrombin times were also prolonged in males at 5000 and 20,000 ppm after 3, 6, and 12 months of treatment and at the high dose after 18 months (24 month values were comparable to controls). Mild increases in group mean gamma-glutamyl transpeptidase activity were noted for both sexes at the mid and high dose levels at 18 and/or 24 months. Group mean urinary protein levels were increased at 6, 12, 18, and 24 months of treatment in high dose females vs controls.

Group mean relative kidney and liver weights were increased in both sexes at the mid and high dose levels after 12 and 24 months of treatment vs controls (statistical significance was noted for both organs of mid and high dose females and high dose males at 12 months and for both organs of mid and high dose females, livers of mid and high dose males, and kidneys of high dose males at 24 months).

Histopathology revealed treatment-related findings in the liver and kidneys (changes were more pronounced in females). Non-Neoplastic Findings. Increases in central lobular hepatocellular hypertrophy (minimal to marked severity) were noted in the liver of both sexes at the mid and high dose level compared to controls (statistical significance at the high dose level for both sexes and for mid dose females) at the 12 month sacrifice (both mid and high dose females had central lobular necrosis and hepatocellular polyploidy (minimal to slight)). At the 24 month sacrifice, central lobular hepatocellular hypertrophy was increased in the liver of both sexes at the mid and high dose levels vs controls (statistically significant in mid and high dose females and in high dose males). Increases in eosinophilic alterations, basophilic alterations, hepatocellular polyploidy, and bile duct epithelial hyperplasia were also noted for both sexes at the mid and high levels compared to controls (with statistical significance in females). At the 12 month interim sacrifice, the incidence of subacute/chronic interstitial inflammation/chronic nephropathy/cysts was increased in kidneys of both sexes at the mid and high dose levels compared to controls (with statistical significance for high dose females). At 24 months, significant increases in subacute/chronic interstitial inflammation/chronic nephropathy/cysts were noted in kidneys of both sexes at the high dose levels and in mid dose females compared to controls. Additionally, at 24 months, a significant increase in the incidence of brown pigment in the cortex/medulla tubular epithelium/reticuloendothelial cells of the kidneys of mid and high dose females was noted vs controls. Neoplastic Findings. Treatment-related increases in neoplasms were limited to the liver. An increase in hepatocellular adenomas in the liver of high dose females was noted at the interim sacrifice vs controls (0/10 for controls vs 2/10) (the incidence for males was 0/10 at the high dose level). At the 24 month sacrifice, the incidence of hepatocellular adenomas in the liver was 1/25, 0/20, 1/20, and 3/21 in males and 1/26, 0/30, 4/32, and 8/44 in females at 0, 500, 5000, and 20,000/10,000 ppm, respectively. The overall incidence of hepatocellular adenomas in the liver was 1/75, 0/75, 1/75, and 4/75 (5.3%) in males and 1/75/ 0/75/, 6/75 (8%), and 12*/75 (16%) in females at 0, 500, 5000, and 20,000/10,000 ppm, respectively (statistical difference from control in high dose females). The overall incidence of hepatocellular carcinomas in the liver was 1/75, 3/75, 1/75, and 1/75 in males and 0/75, 0/75, 0/75, and 1/75 in females at 0, 500, 5000, and 20,000/10,000 ppm, respectively.

No treatment-related effects were noted for mortality, clinical signs, ophthalmology, neurobehavioral effects, or gross pathology.

Volume 53072-0029, records 241638, 241639, 241640, and 241641 contains historical control data for neoplastic and non-neoplastic lesions in 24 month rat studies. Volume 53072-0030, record 241642 is supplemental study performed to investigate the S-phase response (DNA synthesis) in the liver of rats fed BAS 560 F treated diet for up to 4 weeks. Volume 53072-0031, record 241643 is a supplemental study performed to determined the possible tumor-initiating potential of BAS 560 F in rat liver. Volume 53072-0040, record 241659 contains a results summary of 14 week dietary studies with benzophenone (the same chemical class as BAS 560 F (metrafenone)) in F344/N rats and B6C3F$_1$ Mice performed by the National Toxicology Program (NTP) dated April 2002. Volume 53072-0041, record 241660 is a method validation study with the positive control phenobarbital, administered in the diet of Sprague Dawley rats for 4 weeks.

Chronic NOEL = 500 ppm (24.9 mg/kg/day for males and 30.4 mg/kg/day for females) based on reduced bodyweight gain, non-neoplastic liver microscopy, and serum chemistry. **Possible adverse effect:** increased hepatocellular adenomas. Acceptable. (Green, 8/5/09).

Supplemental Data, Combined Rat

53072-0029 241641, "BAS 560 F, Hepatic Enzyme Induction Study in Sprague Dawley Rats, Administration in the Diet for 4 Weeks", (W. Mellert, *et al*., Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, Report/Project No. 99C0437/01053, 9 April 2002). 5 Sprague Dawley rats per sex per group received BAS 560 F (94.2% metrafenone)

in the diet at 0 (basal diet) and 20,000 ppm for 4 weeks. Group mean BAS 560 F intake was 1526 mg/kg/day for males and 1654 mg/kg/day for females at 20,000 ppm over the treatment period. All animals survived with no treatment-related clinical signs. Group mean food consumption for treated females were significantly decreased on days 7, 21, and 28 compared to controls. Group mean water consumption was significantly increased for treated males on day 21. Group mean bodyweight was decreased for treated females throughout the treatment period with statistical significance on day 21 compared to control (the group mean value on day 28 was 8.2% below the control value). Group mean bodyweight gain was decreased throughout the treatment period for treated males with statistical significance on day 7 vs controls (the group mean value on day 28 was 10.1% below the control value). In treated females, group mean bodyweight gain was decreased throughout the study with statistical significance on days 21 and 28 vs controls (the mean value on day 28 was 19.3% below the control results). At the end of the treatment period, animals were sacrificed (decapitation) and the liver of each animal was perfused with 20 ml of 0.9% NaCl-solution via the portal vein, homogenized, and evaluated for peroxisome proliferation (cyanide -insensitive palmitoyl-C0A-oxidation (PALCoA)) and liver enzyme induction (glutathione concentration (GSH), ethoxyresorufin-O-deethylase activity (EROD), and pentoxyresorufin-O-depentylase activity (PROD)). No treatment-related changes were indicated for PALCoA and GSH. PROD activity was slightly but significantly increased (~2 fold) in treated females (male values were comparable to controls). EROD activity indicated treatment related liver enzyme induction with significant increases in treated males (17 fold) and females (10 fold) vs controls. Supplemental data. (Green, 7/29/09). No worksheet.

53072-0030 241642, “BAS 560 F S-Phase Response Study in the Liver of Sprague Dawley Rats, Administration in the Diet for 1 and 4 Weeks and Recovery Period of 2 Weeks”, (W. Wellert, *et al*., Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, Report/Project No. 99C0437/01048, 14 May 2002). 8 Sprague Dawley (Crl:CD (SD)IGS BR) rats per sex per group received BAS 560 F (95.86%) in the diet at 0 (basal diet), 500, and 20,000 ppm for 1 week and 4 weeks. An additional 8 per sex received 20,000 ppm in the diet for 4 weeks followed by a 2 week recovery period receiving untreated basal diet. One week prior to necropsy, osmotic minipumps containing bromodeoxyuridine (BrdU) were implanted subcutaneously. At necropsy (end of the treatment period or recovery period), cell proliferation (S-phase response), apoptosis, and mitosis were evaluated in the liver. Livers were sliced into 2 strips (5 mm thickness, from the right lateral and medial lobes), fixed (4% formaldehyde solution for 24-48 hours, and placed in 70% ethanol). From each strip, 5 sections were cut (3 µm each), 1 section was stained (hematoxylin and eosin), mounted on slides, and evaluated (light microscopy) for an estimation of cell proliferation (the amount of mitotic and apoptotic figures based on morphology). The other 4 sections were used for immunohistology evaluation (light microscopy). One immunohistology section was stained with BrdU (5-bromo2'-deoxy-uridine) stain for S-phase response determination and another with TUNEL stain (terminal deoxynucleotidyl transferase (dUTP) nick end labeling) to detect apoptotic cells and 2 served as negative controls for each stain. Group mean daily BAS 560 F intake was 30 and 1005 mg/kg/day for males and 33 and 814 mg/kg/day for females at 500 and 20,000 ppm, respectively, in the 1 week treatment phase; 27 and 1020 mg/kg/day for males and 32 and 1069 mg/kg/day for females at 500 and 20,000 ppm, respectively , in the 4 week treatment phase; and 1184 mg/kg/day for males and 1242 mg/kg/day for females at 20,000 ppm, respectively, in recovery phase animals. Two incidental deaths occurred: 1 control male (4 week treatment group) died on day 21 and one high dose female (1 week treatment group) died on day 3. No treatment-related clinical signs were indicated. Food consumption was significantly reduced for both sexes at the high dose level in the 1 week treatment phase (-21.9% for males and -44.2% for females on day 7) and the 4 week treatment phase (-18.5% for males on day 7 and -45.8%, -19.6%, -16.1%, and -9.2% on days 7, 14, 21, and 28, respectively, for females) compared to controls. In the 4 week treatment phase, water consumption was significantly increased for high dose males (20.1% to 27.3%) and females (66.4% to 114.3%) on days 7, 14,

21, and 28. Bodyweight was significantly decreased in high dose females in the 1 week treatment phase on day 7 (-9.6%) vs controls and bodyweight change was significantly reduced in low (12.1 g vs 23.5 g for control) and high dose females (-7 g vs 23.5 g for control) and high dose males (9.2 g vs 26 g for control) on day 7 vs controls. In the 4 week treatment phase, bodyweight was significantly reduced for high dose females on days 21 (-9.1%) and 28 (-7.5%) and bodyweight change was significantly reduced for low (23.8 g vs 31.9 g for control on day 28) and high dose females (-18.9 vs -1g on day 7, -15.3 vs 5.3 g on day 14, -12.7 vs 15.6 g on day 21, and 6.8 vs 31.9 g on day 28) and high dose males (8.5 g vs 17.5 g for control on day 7) vs controls. Group mean relative liver weights were significantly increased in high dose males (17%) and females (48%) vs controls in the 1 week treatment phase and for high dose males (15%) and females (65%) in the 4 week treatment phase (relative liver weights were significantly decreased (-8%) in low dose females vs controls). Group mean recovery relative liver weights were comparable to controls for both sexes at the end of the 2 week recovery period. Liver Histopathology. Centrilobular hypertrophy of hepatocytes in the liver (minimal to slight) was increased for high dose males (8/8) and females (5/8) in the 1 week treatment phase animals; in 8/8 males and 7/8 females (minimal to moderate) at the high dose level in the 4 week treatment phase animals (2 females had increased mitotic figures in the periportal region (minimal to moderate)); and no treatment-related liver histopathology was indicated for 4 week treatment with 2 week recovery phase animals. S-Phase Response in the Liver. Relative cell proliferation was significantly increased in the liver of both sexes at 20,000 ppm compared to controls for both the 1 week treatment phase (6.5 fold increases for males and 95.6 fold for females in the periportal section) and for low dose females (3.9 fold increases). 4 week treatment phase females had significant increases in relative periportal cell proliferation of the liver at the high dose level vs control (4.2 fold). Cell proliferation was significantly reduced for recovery phase animals vs controls. Apoptosis in the Liver. Significant increases in the total number of apoptotic cells were noted for low and high dose males in the 1 week treatment groups (values were marginally significant) and for high dose females in the 4 week treatment phase and the 2 week recovery phase. Supplemental data. (Green, 8/3/09). No worksheet.

53072-0031 241643, “BAS 560 F - Initiation Study in Sprague Dawley Rats”, (W. Mellert, *et al*., Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, Report/Project No. 99C0437/01040, 14 May 2002). Duplicate groups of 12 Sprague Dawley (Crl:CD (SD)IGS BR) rats per sex per group received a single oral gavage dose of BAS 560 F (95.86%) at 0 (doubly distilled water) and 5000 mg/kg/day 14 hours after partial hepatectomy (*Lobus sinister lateralis, Lobus sinister medialis,* and *Lobus dexter medialis* were removed) after which animals received basal diet (*ad libitum*) for 14-days (initiation period). Other duplicate groups received a single oral gavage dose of nitrosomorpholine (NNM) at 50 mg/kg/day as a positive control for initiation. After the 14-day initiation period, one duplicate group received basal diet and the other received phenobarbitone (PB) in the diet at 500 ppm for the 8 week promotion period. Necropsies were performed on all surviving animals at the end of the promotion period and livers were weighed. Three sections of all remaining liver lobes (right lateral lobe, caudate process, and papillary process) were cut into 3 mm thick slices and fixed (1 section from each lobe in buffered 4% formalin solution; 2 sections from each lobe in individual cassettes in Carnoy’s solution; and the remaining liver tissue in 4% formalin solution). One section from each lobe fixed in Carnoy’s solution was embedded (paraffin), sectioned (three 4 µm serial sections per lobe), and mounted. For detection of preneoplastic foci, one slide was immunohistochemically stained with an antibody against glutathione S-transferase placental form (GST-P), a second was used as a negative control slide for the immunohistochemical staining, and a third slide was stained with hematoxylin and eosin (H & E). Preneoplastic foci were identified by a positive GST-P reaction (increased foci) and, in H & E stained slides, by phenotypical alteration (cytoplasmic tinctorial variation or altered cell size) and staining properties (clear cell, basophilic, or eosinophilic). Foci numbers, area of foci, and the area of the liver involved were determined (KS400 computer program, Zeiss, Munch, Germany). Group mean

relative liver weights were significantly increased for males that received 5000 mg/kg/day BAS 560 F followed by basal diet during the promotion period. The number of GST-P and H & E positive foci in animals treated with BAS 560 F were comparable to vehicle control values. Positive controls were valid. Tumor initiation was not indicated. Supplemental data. (Green, 8/4/09). No worksheet.

Volume 53072-0040, record 241659 contains a results summary of 14 week dietary studies with benzophenone (in the same chemical class as BAS 560 F (metrafenone)) in F344/N rats and $B6C3F_1$ Mice performed by the National Toxicology Program (NTP) dated April 2002. Groups of 10 male and 10 female F344/N rats and B6c3F1 mice received benzophenone at 0, 1250, 2500, 5000, 10,000, or 20,000 ppm for 14 weeks. Average daily benzophenone intakes were 75 (males) and 80 (females), 150 (males) and 160 (females), 300 (both sexes), 700 (both sexes), or 850 (males) and 1000 mg/kg/day (females) for rats and 200 (males) and 270 (females), 400 (males) and 540 (females), 800 (males) and 1000 (females), 1600 (males) and 1900 (females), or 3300 (males) and 4200 mg/kg/day (females) for mice at 1250, 2500, 5000, 10,000, or 20,000 ppm, respectively, during the 14 week treatment period. The liver was the primary target of treatment with benzophenone in rats and mice, based on increases in liver weights, hepatocellular hypertrophy, clinical chemistry changes, and induction of the liver microsomal cytochrome P450 2B isomer. The kidney was also identified as a target organ in rats, based on dose related increases in kidney weights and microscopic changes. Supplemental data. (Green, 8/5/09). No worksheet.

Volume 53072-0041, record 241660 is a method validation study with the positive control phenobarbital. “Phenobarbital Sodium Salt Hepatic Enzyme Induction Study in Sprague Dawley Rats, Administration in the Diet for 4 Weeks”, (W. Mellert, *et al*., Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, Report/Project No. 99C0191/96205, 9 April 2002). 5 Sprague Dawley (Crl:CD) rats per sex per group received phenobarbital sodium salt (PB) in the diet at 0 and 500 ppm (38.9 mg/kg/day for males and 42.6 mg/kg/day for females) for 4 weeks. At the end of treatment, the following peroxisome proliferation or hepatic enzyme induction parameters were determined: cyanide-insensitive palmitoly-CoA-oxidation (PALCoA), glutathione concentration (GSH), cytochrome P450 content (Cyt. P450), ethoxyresorufin-O-deethylase (EROD), and pentoxyresorufin-O-depentylase (PROD). Cytochrome P450 content and PROD activity were markedly increased, and EROD activity was slightly increased in the liver of both sexes treated with PB. No treatment related effects were indicated for PALCoA or GSH. Supplemental data. (Green, 8/5/09). No worksheet

CHRONIC TOXICITY, RAT

See combined, rat

CHRONIC TOXICITY, DOG

**53072-0027 241636, “One-Year Oral Toxicity Study with BAS 560F in Purebred Beagle Dogs via Capsule Administration”, (C.M. Kelly, Huntingdon Life Sciences, East Millstone, NJ., Laboratory Project ID. 98-3388, 30 November 2001). 4 Beagle dogs per sex per group received BAS 560F (95.86%) by oral administration (gelatine capsule) at 0 (empty capsules), 50, 100, and 500 mg/kg/day for 1year. All animals survived to study termination. Group mean alkaline phosphatase activity (ALK) was generally elevated for treated groups of both sexes after 3, 6, 9 and 12 months of treatment compared to controls and values were generally increased compared to the historical control data (especially for females) presented for the equivalent 3, 6, 9, and 12 month measurement periods. Statistically significant increases in ALK were noted for 500 mg/kg/day males after 9 and 12 months of treatment and for females at 50, 150, and 500 mg/kg/day after 3 months. Group mean relative liver weights were increased for both sexes at 150 and 500 mg/kg/day (and, also at 50 mg/kg/day for females) compared to controls with

statistical significance at the low and high dose in females and at the high dose in males. Absolute liver weights were also increased for males and females at 50, 150, and 500 mg/kg/day compared to controls (with statistical significance in females at 150 and 500 mg/kg/day). No associated macroscopic or microscopic findings were recorded. No treatment related mortality, clinical observations, ophthalmology, bodyweight and bodyweight change, food consumption, hematology, urinalysis, gross pathology, or histology was indicated. NOEL = 500 mg/kg/day. No adverse effect. Acceptable. (Green, 4/15/09).

ONCOGENICITY, RAT

See combined, rat

ONCOGENICITY, MOUSE

****53072-0028, 0040 241637, 241659,** "18-Month Dietary Oncogenicity Study in Albino Mice with BAS 560 F", (J. E. Fischer, BASF Agro Research, Toxicology, Princeton, NJ., Study No. T-1130, Report No. AX01-05.01, 12 March 2002). 65 Crl:CD-1(ICR)BR albino mice per sex per group received BAS 560F (95.86%) in the diet at 0 (basal diet), 250, 1000, and 7000 ppm for 18 months. Group mean average BAS 560F intake was 39, 156, and 1109 mg/kg/day for males and 53, 223, and 1493 mg/kg/day for females at 250, 1000, and 7000 ppm, respectively, during the 18 month treatment period. There was no treatment-related effect on mortality, clinical signs, food consumption, or bodyweight. Group mean hematocrit values were significantly increased for females at 1000 and 7000 ppm at the 12 month sampling (platelets were also significantly increased at the high dose level). A non-statistical increase in the incidence of liver masses was noted in high dose males compared to controls (12/54 vs 5/45). Significant increases were noted in group mean absolute and relative liver weights for high dose males and for mid and high dose females compared to controls. Significant increases in centrilobular and diffuse hepatocellular hypertrophy (minimal to moderate) were noted in the livers of mid (15/65 centrilobular and 6/65 diffuse) and high dose males (34/66 centrilobular and 20/66 diffuse) and high dose females (5/65 centrilobular and 24/65 diffuse) compared to controls (0 incidence in all cases). Significant increases in hepatocellular adenomas were noted for high dose males (14/66) compared to controls (4/65) (a non-statistical increase was also noted for mid dose males (8/65)). Values for high dose females (2/65) were comparable to controls (2/65). The incidence of hepatocellular carcinomas in the liver were 2/65, 1/65, 1/65, and 5/66 for males and 0/65, 0/65, 0/65, and 2/65 for females at 0, 250, 1000, and 7000 ppm, respectively. In kidneys, the incidence and severity of chronic nephropathy was significantly increased for males at the low (52/65), mid (59/65), and high dose levels (64/66) vs controls (42/65) and for high dose females (64/65) vs controls (40/65). In the spleen, a significant increase in extramedullary hematopoiesis was noted in high dose females (32/65) vs controls (20/65) (male values were comparable to controls). Volume 53072-0040, record 241659 contains a results summary of 14 week dietary studies with benzophenone (the same chemical class as BAS 560 F (metrafenone)) in F344/N rats and B6C3F$_1$ Mice performed by the National Toxicology Program (NTP) dated April 2002. Chronic NOEL = 250 ppm (39 mg/kg/day for males and 53 mg/kg/day for females) based on non-neoplastic liver and kidney microscopy. Oncogenicity NOEL = 1000 ppm (156 mg/kg/day for males and 223 mg/kg/day for females) based on increased hepatocellular neoplasms in males. **Possible adverse effect:** increased hepatocellular adenomas. Acceptable. (Green, 8/11/09).

REPRODUCTION, RAT

**53072-0035, 0036 241647, 241648, "A Two-Generation Reproduction Study with BAS 560F in Rats", (R. E. Schroeder, MPI Research Inc., Mattawan, MI, Laboratory Project ID. 141-037, BASF Registration Document No. BN-430-002, 8 March 2002). 30 Sprague-Dawley albino rats

(Crl:CD® (SD)IGS BR) per sex per group received BAS 560F (95.86%) in the diet at 0 (basal diet), 500, 1000, and 10,000 ppm through 2 generations with 1 litter per generation. The average combined BAS 560F intakes for F0 and F1 parental males and females were 39, 79, and 811 mg/kg/day at 500, 1000, and 10,000 ppm, respectively, during the 10-week premating periods.

F0 Parents. At 10,000 ppm, group mean bodyweight was significantly reduced for F0 females vs controls for weeks 7 through 11of the premating period and group mean bodyweight gain was significantly lower vs control during the entire premating period (weeks 1 through 11). Gestation and lactation period group mean bodyweights and bodyweight gains were significantly reduced for F0 females at 10,000 ppm vs controls. Group mean food consumption was significantly reduced for F0 females vs controls during the premating period, the gestation period (days 0 to 7 and 7 to 14), and the lactation period (days 0 to 4, 4 to 7, 7 to 10, and 10 to 14) at the high dose level. At termination, significant decreases were noted in F0 group mean erythrocyte counts, hemoglobin, and hematocrit for both sexes vs controls at 10,000 ppm (the effect was more pronounced in females). At 10,000 ppm, significant increases were noted in the following F0 group mean relative organ weights: liver (both sexes), kidney (both sexes), adrenal glands (females only), and spleen (males only). Group mean relative liver weights were also significantly increased for F0 females at 500 and 1000 ppm. F0 group mean relative thymus weights were significantly decreased for high dose males and for low, mid and high dose females. Histopathology of F0 parents revealed increased incidence of minimal (trace) hepatocellular hypertrophy in liver of high dose males (17/30)and females (26/30) vs controls (0/30).

F1a Offspring. Group mean F1a pup weights were significantly reduced at birth, throughout the lactation period, and during the post lactation period (days 28 and 35) at the high dose level compared to controls. Vaginal opening in F1 parental females was significantly delayed at 10,000 ppm vs controls (34.7 days vs 32.4 days). Group mean relative F1a liver weights were significantly increased vs controls for males and females at 10,000 ppm (and at 1000 ppm in females). Group mean relative F1a spleen and thymus weights were significantly decreased at 10,000 ppm vs controls for both sexes (relative spleen weights were also significantly decreased for low and mid dose females (no dose response)).

F1 Parents. F1 parental group mean bodyweight for both sexes was significantly decreased throughout the study at 10,000 ppm vs controls and for F1 males at 1000 ppm from premating week 6 through the remainder of the study (values for 500 ppm males and females and 1000 ppm females were comparable to controls). Group mean bodyweight gain for F1 males was significantly reduced at the mid and high dose levels vs controls throughout the entire study (weeks 1-21). Group mean bodyweight gain for F1 females at 10,000 ppm was significantly reduced vs controls during the premating period. Group mean bodyweight for F1 females during the gestation and lactation periods was significantly decreased vs controls at 10,000 ppm (group mean bodyweight gain values were comparable to controls). Group mean food consumption was significantly decreased for F1 females at 10,000 ppm during the premating period (weeks 1 through 11), the gestation period (days 0-7 and 7-14), and the lactation period (days 7-10 and 10-14) vs controls (male values were generally comparable to controls during the premating period). F1 parental females had significantly decreased group mean erythrocyte count, hemoglobin, and hematocrit at the mid and high dose levels at termination vs controls (hematocrit was also significantly decreased for high dose males). Group mean F1 relative liver weights were significantly increased for mid and high dose males and females and for low dose males vs controls. Group mean F1 relative thymus were significantly decreased for both sexes at 10,000 ppm compared to controls (and for low and mid dose females) . Significant reductions were noted in primordial follicle counts for F1 females at 1000 and 10,000 ppm. In F1 males at 10,000 ppm, the percent of progressively motile sperm was significantly reduced vs controls and the percent of abnormal sperm (change in appearance of the sperm hook) was significantly increased. At histopathology, minimal (trace) hepatocellular hypertrophy was noted in liver of

high dose F1 males (17/29) and females (25/30) vs controls (0/30).

F2a Offspring. Group mean F2a pup weights were significantly reduced at 10,000 ppm vs controls from birth and throughout the lactation period (pups weighed ~11% less than controls at birth and ~32% less than controls at weaning). At 10,000 ppm, several F2a pups were noted with decreased activity, sparse hair coat, coldness to touch and/or emaciation. On lactation day 21, activated partial thromboplastin times were significantly increased for F2a males (27%) and females (41%) at the high dose compared to control values and prothrombin time was significantly increased for mid dose F2a females (11%). Group mean relative liver weights for F2a pups were significantly increased vs controls at 10,000 ppm (and at 1000 ppm in F2a males). Group mean absolute and relative spleen and thymus weights were significantly reduced at 10,000 ppm compared to controls.

Parental NOEL = 500 ppm (39 mg/kg/day) based on reduced bodyweight. Pup NOEL = 1000 ppm (based on reduced pup weights, delayed development (vaginal opening)). Reproductive NOEL = 10,000 ppm (811 mg/kg/day). No adverse reproductive effects. Acceptable. (Green, 5/21/09).

53072-0035 241647, "A Pilot Dietary Reproduction Study with AC 375839 in Rats", (R.E. Schroeder, MPI Research Inc., Mattawan, MI., Laboratory Project ID. 141-036, BASF Registration Document No. BN-430-001, 21 September 2001). 10 Sprague-Dawley albino rats (Crl:CD® (SD) IGS BR) received AC 375839 (95.86%) in the diet at 0 (basal diet), 500, 1000, and 10,000 ppm for one generation (starting 10 weeks before mating of the F0 animals through post-natal day 29 for F1a animals). FO Parental Animals. During the premating interval, group mean AC 375839 intake was 38.4, 76.3, and 790 mg/kg/day for F0 males and 43.8, 91.3, and 882 mg/kg/day for F0 females at 500, 1000, and 10,000 ppm, respectively. At 10,000 ppm, group mean F0 female bodyweight was slightly reduced vs controls (with statistical significance for weeks 8 and 9) and bodyweight gain was significantly decreased (-11%) vs controls for the premating period. No treatment-related effects on male bodyweight and bodyweight gain. F0 female bodyweight was significantly lower than controls during gestation (days 0, 7, and 14) and lactation (days 0, 4, 7, 14, and 21) at 10,000 ppm (bodyweight gain was comparable to controls for both periods). At the high dose level, group mean F0 female food consumption was reduced for lactation days 0-14 vs controls (with statistical significance for days 7-10). At termination, group mean erythrocyte counts, hemoglobin, and hematocrit for high dose F0 females were slightly lower than controls (F0 male values were comparable to controls). Group mean F0 absolute and relative liver weights were significantly increased for males and females at 10,000 ppm and for 1000 ppm males vs controls. Histopathology revealed increased centrilobular hepatocellular hypertrophy in livers of all high dose F0 males and females (trace to mild in severity) vs controls (3/10 mid dose males showed trace severity). No treatment related effects were noted for clinical signs, mating and fertility parameters, and litter size. F1 Offspring. At 10,000 ppm, group mean pup bodyweights were reduced vs controls (-6% at birth and -21% (statistically significant) at weaning (lactation day 21)) and were significantly decreased vs controls throughout the 1-week postweaning treatment period (post-natal days 22, 25, and 29). Group mean F1a pup food consumption was slightly reduced vs controls (ns) at the high dose level during the 1-week postweaning treatment period. During the 1-week postweaning period, group mean AC 375839 intake for F1a pups was 66, 130, and 1373 mg/kg/day for males and 57, 131, and 1247 mg/kg/day for females at 500, 1000, and 10,000 ppm, respectively. On post-natal day (PND) 29, group mean erythrocyte counts for F1a male pups were significantly reduced vs controls at 10,000 ppm. Group mean relative liver weights were significantly increased for F1a pups sacrificed on PND 29 at 500, 1000 and 10,000 ppm compared to controls and for high dose males and mid and high dose females sacrificed on PND 21. Histopathology of F1a pups sacrificed on post natal day 29 showed an increase in generalized or diffuse hepatocellular hypertrophy (trace to mild severity) in liver of all animals of both sexes at 10,000 ppm. F0 NOEL

= 500 ppm (38.4 mg/kg/day for males and 43.8 mg/kg/day for females) based on increased liver weights and hepatocellular hypertrophy. F1a pup NOEL = 1000 ppm (76.3 mg/kg/day for males and 91.3 mg/kg/day for females) based on reduced pup weights. Reproductive NOEL = 10,000 ppm (790 mg/kg/day for males and 882 mg/kg/day for females). Supplemental data. (Green, 5/11/09). (No worksheet).

TERATOLOGY, RAT

**53072-0034 241646, "A Definitive Oral Developmental Toxicity (Embryo-Fetal Toxicity/Teratogenicity) Study with BAS 560 F in Rats", (J. F. Barnett, Argus Research Laboratories, Inc., Horsham, PA., Study No. 101-035, 21 December 2001). 25 mated female Crl:CD® (SD)IGS BR VAF/Plus® rats per group received BAS 560 F (95.86%) by oral gavage at 0 (aqueous 0.5% carboxymethylcellulose), 50, 500, and 1000 mg/kg/day on gestation days 6 through 20. All dams survived to scheduled sacrifice. Relative maternal liver weights were significantly increased at 1000 mg/kg vs controls. No treatment-related effects were indicated for maternal clinical signs, maternal bodyweights, maternal food consumption, maternal hematology, maternal necropsies and reproductive outcomes, maternal liver histology, litter parameters, or fetal external, visceral and skeletal alterations. Maternal and Developmental NOEL = 1000 mg/kg/day. No teratogenicity. Acceptable. (Green, 6/18/09).

TERATOLOGY, RABBIT

**53072-0033 241645, "A Definitive Oral Developmental Toxicity (Embryo-Fetal Toxicity/Teratogenicity) Study with BAS 560F in Rabbits", (J. F. Barnett, Argus Research Laboratories, Inc., Horsham, PA., Study No. 101-034, 21 December 2001). 25 mated female New Zealand White [Hra:NZW)SPF] rabbits per group received BAS 560F (95.86%) by oral gavage at 0 (aqueous 0.5% carboxymethylcellulose), 50, 350, and 700 mg/kg/day on gestation days 6 through 28. One control and one high dose female were found dead on gestation days 15 and 10, respectively, and one control female was sacrificed moribund on day 21 (all 3 deaths were attributed to intubation accidents). One mid dose and 2 high dose females delivered on gestation day 29 prior to sacrifice and one control and one high dose female aborted on days 26 and 28, respectively (necropsy results were unremarkable). The incidence of scant feces was significantly increased at 700 mg/kg/day compared to controls. Group mean maternal bodyweight gains and food consumption were significantly reduced at 350 and 700 mg/kg/day during the treatment period compared to controls. Group mean maternal prothrombin and activated partial thromboplastin times were significantly increased at 700 mg/kg/day vs controls. Group mean maternal relative liver weights were significantly increased at the mid and high dose level vs controls. Histopathology revealed a dose-dependent increase in the incidence and severity of periportal hepatocellular hypertrophy and diffuse hepatocellular vacuolation in the liver of females treated at 350 and 700 mg/kg/day vs controls. Group mean fetal weights were significantly reduced at 700 mg/kg/day vs controls. No treatment-related fetal external, visceral, or skeletal effects were indicated. Maternal NOEL = 50 mg/kg/day (based on reduced bodyweight gain and food consumption). Developmental NOEL = 350 mg/kg/day (based on reduced fetal weights). Teratogenicity was not indicated. Acceptable. (Green, 6/24/09).

GENE MUTATION

**53072-0037 241649, "Bacterial Reverse Mutation Assay with AC 375839", (V. O. Wagner, III and J. E. Sly, BioReliance, Rockville, MD., Study No. AA11JE.502.BTL, 14 June 1999). Triplicate cultures of *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 uvrA were exposed (direct plate incorporation) to AC 375839

(95.86%), in the presence and absence of S9 mix, at 0 (DMSO), 25, 50, 100, 250, 500, 1000, 2500, and 5000 µg/plate for 48 to 72 hours (37 ± 2°C). There was no increase in the number of revertants per plate and cytotoxicity was not indicated. Precipitation was noted at 1000 µg/plate and above. Positive controls were functional. Acceptable. (Green, 6/8/09).

**53072-0037 241650, "BAS 560F: Test for Chemical Induction of Gene Mutation at the HGPRT Locus in Cultured Chinese Hamster Ovary (CHO) Cells With and Without Metabolic Activation with a Confirmatory Assay", (K. J. Pant, SITEK Research Laboratories, Rockville, MD, Study No. 0645-2510, 10 August 2001). Duplicate cultures (3 x 10^6 cells/flask) of Chinese hamster ovary cells (CHO-K1-BH4) were exposed to BAS 560F (95.86%), in the presence and absence of S9 mix, at 0 (DMSO), 17, 50, 167, 500, 1667, and 5000 µg/ml for 4 hours at 37° ± 1°C. A confirmatory assay was performed. No increase in forward mutations was indicated. Positive controls were functional. Acceptable. (Green, 6/9/09).

CHROMOSOME EFFECTS

**53072-0037 241651, "BAS 560F: Test for Chemical Induction of Chromosome Aberration in Cultured Chinese Hamster Ovary (CHO) Cells With and Without Metabolic Activation", (J. Xu, SITEK Research Laboratories, Rockville, MD, Study No. 0645-3110, 28 September 2001). Duplicate cultures (500,000 cells each) of Chinese hamster ovary cells (CHO-W-B1) were exposed to BAS 560F (95.86%) at 0 (untreated, water only), 0 (DMSO), 2.5, 10, 12.5, 25, or 100 µg/ml in the absence of S9 mix and at 0 (untreated), 0 (DMSO), 10, 12.5, 125, and 250 µg/ml with S9 mix. Exposure was for 3 hours and cells were harvested 18 hours after the start of treatment. In the initial assay, chromosome aberrations were scored from the cultures treated at 10, 12,5, and 25 µg/ml (with relative mitotic index (RMI) values of 83%, 77%, and 47%, respectively) in the absence of S9 mix and at 10, 12.5, and 125 µg/ml (with RMI values of 98%, 84%, and 41%, respectively) with S9 mix, respectively. In the confirmatory assay (without activation), chromosome aberrations were scored from the cultures treated at 2.5, 10, and 25 µg/ml (with RMI values of 73%, 61%, and 23%, respectively). No increase in structural chromosome aberrations was indicated. Positive controls were functional. Acceptable. (Green, 6/12/09).

**53072-0037 241652, "AC 375839: In Vivo Test for Chemical Induction of Micronucleated Polychromatic Erythrocytes in Mouse Bone Marrow Cells", (J. Xu, SITEK Research Laboratories, Rockville, MD, Study No. 0622-1521, 11 January 2001). 5 CD-1mice per sex per group received a single oral gavage dose of AC 375839 (95.86%) at 0 (DMSO), 500, 1000, and 2000 mg/kg followed by bone marrow sampling 24, 48, and 72 hours later. No animals died after treatment. 2000 polychromatic erythrocytes per animal were scored for micronuclei. There was no increase in micronucleated polychromatic erythrocytes. Positive controls were functional. Acceptable. (Green 6/15/09).

DNA DAMAGE

**53072-0037 241653, "In Vivo Unscheduled DNA Synthesis (UDS) Assay with BAS 560 F (Metrafenone) in Rat Hepatocytes, Single Oral Administration", (M. Schulz and R. Landsiedel, Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen, Germany, Report No. 80M0437/014217, 24 August 2006). 3 male Wistar Crl:WI (Han) rats per group received a single oral gavage dose of BAS 560 F (99.4%) at 0 (corn oil), 1000, and 2000 mg/kg. Hepatocytes were sampled 3 and 14 hours after treatment. Viability of the hepatocytes was determined using trypan blue and ranged from 97.3% to 102.1%. After attachment, cells were exposed to ^{3}H thymidine for 4 hours followed by 12 hours of incubation with unlabelled thymidine. Six cultures were initiated per animal and 2 or 3 autoradiographs were prepared. 100 cells per animal were analyzed. There was no increase in net nuclear grain counts. Positive controls were functional. Acceptable. (Green, 6/16/09).

SUBCHRONIC STUDIES

Dog Subchronic Oral Toxicity Study

**53081-0024,0025 241633, 241634, "90-Day Oral Toxicity Study with AC 375839 in Purebred Beagle Dogs via Capsule Administration", (C.M. Kelly, Huntingdon Life Sciences, East Millstone, NJ., Laboratory Project ID. 98-3387, 8 January 2002). 4 Beagle dogs per sex per group received AC 375839 (95.86%) by oral administration (gelatine capsule) at 0 (empty capsules), 50, 100, and 500 mg/kg/day for 90 days. All animals survived to terminal sacrifice. Group mean relative liver weights were increased for both sexes at 50, 100, and 500 mg/kg/day compared to controls (with statistical significance in both sexes at the high dose level and in females at 100 mg/kg/day). Group mean absolute liver weights were increased for both sexes at the mid and high dose levels and for low dose males compared to controls (with statistical significance for high dose males). No associated macroscopic or microscopic findings were reported. No treatment-related effects were noted for clinical signs, detailed physical exams, ophthalmology, bodyweight, food consumption, hematology, serum chemistry, urinalysis, gross pathology, and histology. NOEL = 500 mg/kg/day. No adverse effect. Acceptable. (Green, 4/15/09).

Rat 4 Week Subchronic Dermal Toxicity Study

**53072-0026 241635, "BAS 560F - Repeated Dose Dermal Toxicity Study in Wistar Rats, Administration for 4 Weeks", (U. Kaspers, *et al*., Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, Laboratory Project/Report No. 33S0437/01100, 11 November 2003). 10 CrlGlxBrlHan:WI Wistar rats per sex per group were dermally treated (clipped, unabraded, occluded) with BAS 560F (94.2%) at 0 (aqueous 0.5% carboxymethylcellulose), 100, 300, and 1000 mg/kg/day for 4 weeks (6 hours per day, 5 days per week). No treatment-related effects were indicated for mortality, clinical observations, food consumption, water consumption, bodyweight, ophthalmology, hematology, serum chemistry, urinalyses, organ weights, gross pathology, or histology. Dermal and systemic NOEL = 1000 mg/kg/day. Acceptable. (Green, 5/28/09).

Rat Subchronic 13-Week Dietary Toxicity Studies

**53072-0021, 0022 241628, 241629, "13-Week Dietary Toxicity and 28-Day Recovery Study in Albino Rats with BAS 560F", (J. E. Fischer, BASF Agro Research, Toxicology, Princeton, NJ., Laboratory Project ID: T-1046, Toxicology Report No. AX01-01, 25 June 2001). 10 Crl:CD®(SD)BR strain (Sprague-Dawley derived) rats per sex per group received BAS 560F (97.1%) in the diet at 0 (basal diet), 1000, 5000, 10,000, and 20,000 ppm for 13 weeks (5 additional control and high dose animals per sex per group were also treated for 13 weeks, followed by a 28-day recovery phase (untreated diet)). Group mean average daily BAS 560F intakes were 79, 404, 800, and 1663 mg/kg/day for males and 94, 486, 967, and 1938 mg/kg/day for females at 1000, 5000, 10,000, and 20,000 ppm, respectively, during the treatment period. Food consumption in females was slightly decreased (ns) at 1000 (-4.2%) , 5000 (-3.5%), 10,000 (-2.9%), and 20,000 ppm (-3.1%) compared to controls during the treatment period. Male food consumption was slightly increased vs controls at all treatment levels (statistically significant at the high dose level). During the 28-day recovery phase, food consumption for both sexes at the high dose level was comparable to controls. Group mean female bodyweights were significantly decreased during each of the last 7 weeks of the treatment phase at 5000, 10,000, and 20,000 ppm vs controls. Overall group mean bodyweight gain for females during the treatment phase was significantly decreased at 5000 (-14.6%), 10,000 (-14.6%), and 20,000 ppm (-13.2%) compared to controls. Bodyweight gain for both sexes was comparable to controls at 20,000 ppm during the recovery phase. Slight, significant increases in group mean cholesterol and total protein were noted for both sexes at 5000, 10,000, and 20,000 ppm (albumin values were also

significantly increased for high dose females) at the end of the treatment phase compared to controls (values were comparable to controls for both sexes at the high dose level at the end of the recovery phase). Significant increases in group mean urinary protein levels were recorded for 10,000 and 20,000 ppm males at the end of the treatment phase compared to controls (values were within the historical control range). High dose urinalysis results for both sexes were comparable to controls at the end of the recovery period. At the end of the treatment phase, group mean absolute and relative liver weights were significantly increased for males and females at 5000, 10,000, and 20,000 ppm compared to controls (correlated to microscopic changes in females and high dose males). Absolute and relative liver weights were also slightly increased for both sexes at 1000 ppm (with statistical significance for relative values in males). At the end of the 28-day recovery phase, absolute and relative liver weights for high dose animals were comparable to control values. Group mean relative adrenal and heart weights were significantly increased for females at 5000, 10,000, and 20,000 ppm compared to controls at the end of the treatment phase (heart weights were also significantly increased at 1000 ppm). Group mean relative kidney weights were significantly increased in both sexes at 10,000 and 20,000 ppm and for females at 5000 ppm vs control values at the end of the treatment period (absolute kidney weights were also statistically increased for males) (no corresponding microscopic changes were recorded). Heart, adrenal gland, and kidney weights were generally comparable to controls at the end of the recovery phase (except relative kidney weights in high dose females were significantly increased vs controls). Treatment-related liver histology included increased periportal cytoplasmic vacuolation, consistent with the accumulation of lipid, in females at 5000, 10,000, and 20,000 ppm and in males at the high dose level at the end of the treatment phase relative to controls (severity grades were minimal to slight/mild to moderate in females and minimal to slight/mild in males and a dose-response effect was not indicated). At the end of the 28-day recovery phase, minimal to slight/mild periportal cytoplasmic vacuolation was noted in high dose females (high dose males showed no liver effects) vs controls. NOEL = 1000 ppm (79 mg/kg/day for males and 94 mg/kg/day for females) based on increased total protein and cholesterol, decreased bodyweight gain, and increased cytoplasmic vacuolation in the liver. No adverse effect. Acceptable. (Green, 4/23/09).

53072-0022 241630, “13-Week Dietary Toxicity Study in Albino Rats with BAS 560F”, (J. E. Fischer, BASF Agro Research, Toxicology, Princeton, NJ., Laboratory Project ID: T-1079, Toxicology Report No. AX01-03, 30 July 2001). 10 Crl:CD(SD)BR rats per sex per group received BAS 560F (97.1%) in the diet at 0 (basal diet), 250, and 500 ppm for 13 weeks. Group mean average daily intakes of BAS 560F were 21 and 43 mg/kg/day for males and 24 and 48 mg/kg/day for females at 250 and 500 ppm, respectively, during the 13-week treatment period. No treatment related effects on survival, clinical signs, food consumption, bodyweight, bodyweight gain, hematology, serum chemistry, urinalysis, gross pathology, or histology were recorded. NOEL = 500 ppm (43 mg/kg/day for males and 48 mg/kg/day for females). No adverse effect. Supplemental data. (Green, 4/27/09).

Mouse Subchronic 13-Week Dietary Toxicity Studies

**53072-0023 241631, “13-Week Dietary Toxicity Study in Albino Mice with BAS 560F”, (J. E. Fischer, BASF Agro Research, Toxicology, Princeton, NJ., Laboratory Project ID: T-1047, Toxicology Report No. AX01-02, 25 June 2001). 10 albino Crl CD-1(ICR)BR mice per sex per group received BAS 560F (97.1%) in the diet at 0 (basal diet), 1000, 3500, and 7000 ppm for 13 weeks. Group mean average daily BAS 560F intakes were 163, 622, and 1206 mg/kg/day for males and 216, 788, and 1663 mg/kg/day for females at 1000, 3500, and 7000 ppm, respectively, during the treatment period. Group mean male bodyweight was slightly decreased (not statistically significant) at 7000 ppm compared to controls beginning at treatment week 5. Group mean bodyweight gain was reduced (19.8%, ns) for high dose males during the treatment period vs controls. Bodyweights and bodyweight gain for low and mid dose groups and for high

dose females were comparable to controls. Group mean total bilirubin values were increased at 3500 ppm and 7000 ppm for males and females vs controls (with statistical significance in males). Values were within the historical control range. Group mean cholesterol values were significantly increased in high dose females (values were higher than the historical control range). Group mean absolute and relative liver weights were significantly increased for both sexes at 3500 and 7000 ppm (and slightly increased (not statistically significant) at 1000 ppm) compared to controls. Relative values indicated a dose response. Histopathology revealed an increase in centrilobular hepatocellular hypertrophy in the livers of 3500 and 7000 ppm males and females (incidence and severity increased with dose). NOEL = 1000 ppm (163 mg/kg/day for males and 216 mg/kg/day for females) based on increased total bilirubin values and hepatocellular hypertrophy. No adverse effect. Acceptable. (Green, 5/6/09).

53072-0023 241632, "13-Week Dietary Toxicity Study in Albino Mice with BAS 560F", (J. E. Fischer, BASF Agro Research, Toxicology, Princeton, NJ., Laboratory Project ID: T-1085, Toxicology Report No. AX01-04, 30 July 2001). 10 albino Crl:CD-1(ICR)BR mice per sex per group received BAS 560F (97.1%) in the diet at 0 (basal diet), 250, and 500 ppm for 13 weeks. Group mean daily average intakes of BAS 560F were 42 and 84 mg/kg/day for males and 55 and 113 mg/kg/day for females at 250 and 500 ppm, respectively, during the 13-week treatment period. Group mean female bodyweights were slightly decreased (not statistically significant) at 250 and 500 ppm at several measurement intervals compared to controls (no dose response). Overall female bodyweight gains were slightly reduced at 250 ppm (-20.1%) and 500 ppm (-14.8%) compared to controls for the 13-week treatment period (ns). Male bodyweight and bodyweight gains were generally comparable to controls. No treatment-related effects were noted for clinical signs, food consumption, hematology, serum chemistry, organ weights, gross pathology, or histology. NOEL = 500 ppm (84 mg/kg/day for males and 113 mg/kg/day for females). No adverse effect. Supplemental data. (Green, 5/7/09).

NEUROTOXICITY

**53072-0019 241626, "Acute Oral Neurotoxicity Study in Wistar Rats, Single Administration by Gavage", (U. Kaspers, *et al*., Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, Laboratory Project/Report No. 20S0437/01101, 9 July 2003). 10 Wistar CrlGlxBrlHan:WI rats per sex per group received a single oral gavage dose of BAS 560F (94.2%) at 0 (doubly distilled water and/or 0.5% carboxymethylcellulose), 125, 500, and 2000 mg/kg followed by a 14-day observation period. All animals survived to necropsy. Treatment-related effects were not indicated for clinical signs, bodyweight, the functional observational battery, motor activity, gross pathology, and histology. Systemic NOEL = 2000 mg/kg. Neurotoxicity NOEL = 2000 mg/kg. No adverse effect. Acceptable. (Green, 5/4/09).

**53072-0020 241627, "BAS 560F - Subacute Neurotoxicity Study in Wistar Rats; Administration in the Diet for 4 Weeks", (U. Kaspers, *et al*., Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, Laboratory Project/Report No. 30S0437/01109, 26 September 2003). 10 Wistar CrlGlxBrlHan:WI rats per sex per group received BAS 560F (94.2%) in the diet at 0 (basal diet), 1500, 5000, and 15,000 ppm for 4 weeks. Group mean daily BAS 560F intake during the treatment period was 143.0, 458.7, and 1370.9 mg/kg/day for males and 151.9, 492.5, and 1371.1 mg/kg/day for females at 1500, 5000, and 15,000 ppm, respectively. All animals survived to study termination. Piloerection was noted in 2 males and 1 female at 5000 ppm and in 3 males at the high dose level beginning on day 15. Discolored urine (red) was recorded for 1 mid dose and 5 high dose females from day 15. Group mean food consumption was significantly reduced in high dose males (on days 7 and 14) and females (throughout the treatment period). Group mean bodyweight was significantly reduced for high dose males on days 7 and 14. Group mean bodyweight gain was also significantly reduced for high dose males (days 7, 14, and 21) and females (days 14 and 28).

Treatment related effects on the functional observational battery (except piloerection was noted in 3 high dose males on day 27), motor activity, organ weight, gross pathology, or histopathology were not indicated. Systemic NOEL = 1500 ppm (143.0 mg/kg/day for males and 151.9 mg/kg/day for females) based on piloerection. Neurotoxicity NOEL = 15,000 ppm (1370.9 mg/kg/day for males and 1371.1 mg/kg/day for females). No adverse effect. Acceptable. (Green, 4/29/09).

METABOLISM

**53072-0038 241654, "BAS 560 F (AC 375839) Absorption, Distribution, Metabolism, and Excretion Study in the Rat", (N. M. Mallipudi, BASF Corporation, BASF Agro Research, Princeton, NJ, and XenoBiotic Laboratories, Incorporated (XBL), Plainsboro, NJ, Report No. MET 02-003, 30 April 2002). 2, 4, 5, or 12 Sprague Dawley (Crl CD BR) albino rats per sex per group received a single oral gavage dose of [bromophenyl-6-^{14}C]BAS 560 F at 10 mg/kg or [trimethoxyphenol-U-^{14}C]BAS 560 F at 10 and 1000 mg/kg followed by 3 or 7 day observation periods with timed sampling intervals for feces, urine, plasma, bile (bile cannulated rats), and tissue collection at sacrifice. One group of 12 rats per sex received unlabeled BAS 560 F by oral gavage at 10 mg/kg/day for 14 consecutive days following by a single oral gavage dose of [trimethoxyphenol-U-^{14}C]BAS 560 F at 10 mg/kg on the 15th day. After dosing with radiolabel, each rat was placed in an individual metabolism cage.

No differences were indicated in the absorption, elimination and distribution of radioactivity following dosing with ^{14}C BAS 560 F labeled at the 2 different positions. Generally, feces were the major route of excretion (84.09% to 98.83%) after dosing (with urine as a secondary route (0.51% to 14.09%) of dose). Negligible amounts (0.05% to 0.15% of dose) were detected in expired air. Bile was the major route of elimination after a single low dose ([trimethoxyphenol-U-^{14}C] BAS 560 F at 10 mg/kg) in bile cannulated rats (with group mean values of 90.09% (males) and 85.23% (females) of dose) during 72 hours postdosing. Group means of 6.46% (males) and 10.81% (females) of dose were eliminated in feces, and 1.23% (males) and 3.14% (females) in urine during 72 hours (most radiolabel elimination occured during 24 hours), and 0.22% (males) and 0.34% (females) of dose were recovered from tissues after sacrifice of bile cannulated rats. At the high dose in bile cannulated rats ([trimethoxyphenol-U-^{14}C] BAS 560 F at 1000 mg/kg), group mean elimination of radioactivity was highest in feces (81.88% (males) and 79.79% (females), 14.76% (males) and 17.39% (females) in bile, 0.16% (males) and 0.84% (females) in urine during 72 hours postdosing (with most radiolabel eliminated during 48 hours), and 0.05% (males) and 0.11% (females) was recovered from tissues after sacrifice.

Tissue accumulation of radioactivity was mainly in the GI tract and contents at the first sampling time (> 70%) and decreased, thereafter, so that very little radiolabel remained in tissues at 168 hours post dosing. Notable levels of radioactivity were also found in liver, kidneys, muscle, fat, adrenal glands, and blood (plasma and RBC).

BAS 560 F was absorbed quickly into the blood and reached maximum concentrations (C_{max}) of 1.25 µg/g (males) and 1.22 µg/g (females) at 8.5 hours (males) and 11 hours (females) after oral dosing at 10 mg/kg (T_{max}) and, at 1000 mg/kg, C_{max} values at T_{max} were 16.14 µg/g (males) and 12.74 µg/g (females) at 14 hours (males) and 15 hours (females), respectively. The elimination half life ($T_{1/2\ elim}$) was 42.66 hours (males) and 39.03 hours (females) at the low dose level and 54.30 hours (males) and 45.32 hours (females) at the high dose level, respectively. Total blood exposure (i.e., the area under curve from time 0 to observed infinity ($AUC_{0-\infty}$) was 51.16 µg•hr/g (males) and 55.97 µg•hr/g (females) at 10 mg/kg and 930.41 µg•hr/g (males) and 826.73 µg•hr/g (females) at 1000 mg/kg.

Metabolites consisted of glucuronic acid conjugates in bile and urine. Components in feces

consisted primarily of BAS 560 F and aglycones of bile and urine conjugates. ^{14}C BAS 560 F was extensively metabolized in fat, muscle, kidney, and liver resulting in the presence of parent BAS 560 F and glucuronic acid conjugates. The proposed metabolic pathway for BAS 560 F is O-dealkylation, aliphatic oxidation, debromination, ring hydroxylation, and conjugation. Proposed structures for components/metabolites were included along with a structural diagram of the proposed metabolic pathway. Acceptable. (Green, 8/27/09).

**53072-0039 241658, "^{14}C-BAS 560 F - Study of the Dermal Absorption in Rats", (E. Leibold and B. van Ravenzwaay, Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, Report No. 01B0493/016019, 27 February 2002). Two groups of 12 male Sprague-Dawley rats per group received a single, non-occluded (mesh covered) dermal application of [Bromobenzoyl-6-^{14}C] BAS 560 02 F (BAS 560 F 500 g/l SC), 488 g metrafenone per liter (~40.99% - 42.00%) for 10 hours. One group received undiluted [^{14}C] BAS 560 02 F at 5.0 mg/cm^2; the other group were treated with an aqueous dilution at 0.0025 mg/cm^2. After treatment, animals were placed into individual metabolism cages to collect excreta. 10 hours after dosing, the application sites on all rats were washed with a mild soap solution (application sites were redressed (new gauze and bandage) for animals continuing under observation). Excreta were collected for 0 to 10 hours, 0 to 24 hours, and 0 to 168 hours after treatment (cages were rinsed and the rinse collected at the end of each interval). 4 rats per group were sacrificed 10 hours, 24 hours, and 168 hours after the dose application. At each sacrifice, urine, feces, cage wash, blood cells, plasma, kidneys, liver, carcass, treated and surrounding skin, and the protective coverings (including the silicone ring) were analyzed for percentage of administered radioactivity by liquid scintillation counting (LSC).
After the undiluted dose (5.0 mg/cm^2), the majority of administered radioactivity was recovered from the skin wash (group mean values of 96.56% at 10 hours, 89.26% at 24 hours, and 93.40% at 168 hours). The protective cover contained 0.56 %, 1.06%, and 1.54% of dose; the skin of the application site 2.91%, 1.67%, and 0.38% of dose; and the surrounding skin 0.42%, 0.41%, and 0.10% of dose at 10, 24, and 168 hours, respectively. The amount of radiolabel absorbed (including excreta, cage wash, tissues/organs and carcass) was 0.15% (10 hours), 0.23% (24 hours), and 1.15% (168 hours). The highest tissue concentration was in carcass, 0.13% (10 hours), 0.14% (24 hours), and 0.49% (168 hours). Absorbed radioactivity was excreted mainly in feces, 0.00% (10 hours), 0.05% (24 hours), and 0.52% (168 hours).

After treatment with the diluted dose (0.0025 mg/cm^2), skin wash contained most of the recovered dose, 81.76% (10 hours), 80.13% (24 hours), and 87.08% (168 hours). 0.86% (10 hours), 1.02% (24 hours), and 2.53% (168 hours) of dose were recovered from the protective cover, 4.44% (10 hours), 1.01% (24 hours), and 0.23% (168 hours) from the skin of the application site, and 0.26% (10 hours), 0.10% (24 hours), and 0.17% (168 hours) from the surrounding skin. 14.70% (10 hours), 15.22% (24 hours), and 18.72% (168 Hours) was absorbed (includes excreta, cage wash, tissues/organs and carcass). 0.44% (10 hours), 3.27% (24 hours), and 12.60% of dose were excreted in feces. Carcass contained 13.67% (10 hours), 11.25% (24 hours), and 4.92% (168 hours) of dose; liver had 0.31% (10 hours), 0.20% (24 hours), and 0.06% (168 hours) of dose. This study was performed based on an OECD guideline protocol that fits within the parameters of US EPA guidelines for percutaneous absorption testing. Acceptable. (Green, 9/2/09).