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

# SUMMARY OF TOXICOLOGY DATA

Penflufen

**Chemical Code #** 6093 **, Document Processing Number (DPN)** 53185
**SB 950 #** NA
4/23/13
Revised: 1/11/16

## DATA GAP STATUS

| | |
|---|---|
| **Chronic toxicity, rat:** | No data gap, possible adverse effect |
| **Chronic toxicity, dog:** | No data gap, no adverse effect |
| **Oncogenicity, rat:** | No data gap, no adverse effect |
| **Oncogenicity, mouse:** | No data gap, no adverse effect |
| **Reproduction, rat:** | No data gap, no adverse effect |
| **Developmental toxicity, rat:** | No data gap, no adverse effect |
| **Developmental toxicity, rabbit:** | No data gap, no adverse effect |
| **Gene mutation:** | No data gap, no adverse effect |
| **Chromosome effects:** | No data gap, no adverse effect |
| **DNA damage:** | No data gap, no adverse effect |
| **Neurotoxicity:** | No data gap, no adverse effect |

Toxicology one-liners are attached.

All record numbers for the above study types through record no. 287881 (Document No. 53185-0055) were examined. This includes all relevant studies indexed by DPR as of 1/11/16.

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

File name: T160111
Revised by T. Moore, 1/11/16

NOTE: The following symbols may be used in the Table of Contents which follows:
* = data adequately address FIFRA requirement
† = study(ies) flagged as "possible adverse effect"
N/A = study type not currently required

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

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## METABOLISM AND PHARMACOKINETICS

53185-0043 267345, "[Phenyl-UL-$^{13}C_6$/$^{14}C$]BYF 14182: Absorption, Distribution, Excretion and Metabolism in the Rat," ( R. Bongartz and D. Miebach, Bayer CropScience AG, Development, Environmental Safety Metabolism/ADME and Environmental Fate, Monheim am Rhein, Germany, Report No. MEF-08/175, July 13, 2009). Four male or female Wistar Unilever HsdCpb:WU rats per group received a single oral gavage dose of [Phenyl-UL-$^{13}C_6$/$^{14}C$]BYF 14182 at 2 or 200 mg/kg. Test groups 1 (males), 2 (females), and 4 (bile-duct cannulated males) received 2 mg/kg, while test group 3 (males) received 200 mg/kg. In Test groups 1, 2, and 3, urine, feces, and plasma were sampled through 72 hours followed by sacrifice. Urine, feces, and bile were sampled through 48 hours for Test group 4 animals followed by sacrifice. Mean values of 93.9% (test 2) to 97.2% (test 4) of administered radiolabel were recovered from plasma, bile, urine, feces, and organs and tissues across the test groups. The main route of excretion in test numbers 1, 2, and 3 was in the feces (means of 66.77%, 46.00%, and 61.10% of administered dose were noted respectively during 72 hours). In bile-duct cannulated rats, a mean value of 69.94% of administered dose during 48 hours was noted in bile and feces accounted for 5.21% of dose. Mean excretion of administered dose in urine was 27.89%, 47.28%, 33.61%, and 20.96% in tests 1, 2, 3, and 4 respectively. The mean measured maximum concentration of radiolabel in plasma ( $C_{max}$) was 0.74 and 0.75 µg/ml for test 1 and 2 (2 mg/kg dose) and 19.19 µg/ml for test 3 (200 mg/kg) respectively, while the mean measured time to $C_{max}$ ($T_{max}$) was 0.67, 1.00, and 1.5 hours for tests 1, 2, and 3 respectively. Group mean area under the curve values ($AUC_{0-\infty}$) for radiolabel exposure at the low dose level were 2.5 mg/L*h for males (Test 1) and 3.6 mg/L*h for females (Test 2) (high dose values (200 mg/kg) for males were not calculated). The group mean elimination half life at the beginning of the test ($t_{1/2\ elim\ 1}$) was fast at the low dose, 23.6 hours for males and 20.4 hours for females (high dose values were not calculated). Generally, mean concentrations in organs of high dose animals

were ~100 times higher compared to both low dose group test results. Mean % of administered dose in carcass + the gastrointestinal track (GIT) at sacrifice was 0.394% (test 1), 0.585% (test 2), 1.795% (test 3), and 1.060% (test 4). The highest group mean equivalent concentrations of radiolabel were found in liver (~0.02 to 0.06 µg/g at the low dose and ~6.15 µg/g at the high dose) and kidney (~0.02 µg/g at the low dose and ~3.14 µg/g at the high dose). Amounts between 0.04 µg/g (low dose) and 6.74 µg/g (high dose) were found for erythrocytes. Radiolabel residues were very low (0.001 to 0.011 µg/g) in the other organs of the low dose tests, while high dose residues for other organs ranged from 0.4 to 1.9 µg/g. Metabolites in bile, urine, and feces were quantified (radio-HPLC). Parent compound, BYF 14182 was detected in low amounts (≤ 1.79% of administered dose) in feces only. The majority of metabolites (representing 62.7% to 79.4% of administered dose) were identified, and 42 (test 1), 25 (test 2), 35 (test 3) and 32 (test 4) metabolites were characterized. The same metabolites were found in both males and females, but sex-related differences in quantity of some were noted (examples include BYF 14182-desmethyl-dihydroxy-ketone represented 5% and 17% and BYF 14182-desmethyl-pentanoic acid represented 1% and 8% of the administered low dose for males and females respectively). An overview of the principal metabolic reactions of [Phenyl-UL-$^{13}C_6$/$^{14}C$]BYF 14182 in rats along with the schematic of the proposed metabolic pathway were included. Supplemental data. (Green, 4/3/13).

53185-0043 267346, "[Pyrazole-3-$^{14}C$]BYF 14182: Absorption, Distribution, Excretion and Metabolism in the Rat," ( R. Bongartz and D. Miebach, Bayer CropScience AG, Development, Environmental Safety, Metabolism/ADME and Environmental Fate, Monheim am Rhein, Germany, Report No. MEF-08/176, May 26, 2009). Four male Wistar Unilever HsdCpb:WU rats received a single oral gavage dose of [Pyrazole-3-$^{14}C$]BYF 14182 at 2 mg/kg followed by sacrifice 72 hours later. Urine was sampled 4, 8, 12, 24, 48, and 72 hours post-dosing. Feces were sampled 24, 48, and 72 hours after treatment. Plasma was sampled 10, 20, 40, 60, and 90 minutes and 2, 3, 4, 6, 8, 24, 28, 32, 48, 56, and 72 hours after treatment. A mean value of 94.6% of administered radiolabel was recovered in plasma, urine, feces and organs and tissues. The main route of excretion was in the feces with a mean value of 66.59% of dose. Excretion in urine accounted for a mean of 27.61% of dose, and the body including the gastrointestinal tract contained a mean of 0.40%. The mean measured maximum concentration of radiolabel in plasma ( $C_{max}$) was 0.59 µg/ml, while the mean measured time to $C_{max}$ ($T_{max}$) was 0.67 hours post-treatment. The group mean area under the curve value ($AUC_{0-\infty}$) for radiolabel exposure was 2.4 mg/L*h. The group mean elimination half life in plasma at the beginning of the test ($t_{1/2\ elim\ 1}$) was fast, 23.1 hours. The highest group mean equivalent concentrations of radiolabel were found in liver (0.044 µg/g). Moderate mean equivalent concentrations were found in erythrocytes (~0.037 µg/g), thyroid gland (~0.019 µg/g), and kidney (~0.017 µg/g). Radiolabel residues were very low (~0.0016 to 0.0067 µg/g) in the other organs. Metabolites in urine and feces were quantified (radio-HPLC). Parent compound, BYF 14182 was detected in low amounts (0.47% of administered dose) in feces only. The majority of metabolites, representing 68.72% of administered dose, were identified, and 41 metabolites, representing 20.06% of dose, were characterized. Approximately 18% of the dose was identified as trihydroxy compounds and ~9% as dihydroxy compounds. Oxidation of the hydroxy groups resulted in keto compounds (~25% of the dose) or carboxylic acids (~23% of the dose). An overview of the principal metabolic reactions of [Pyrazole-3-$^{14}C$]BYF 14182 in rats along with the schematic of the proposed metabolic pathway were included. Supplemental data. (Green, 4/4/13).

53185-0043 267349, "Quantitative Whole Body Autoradiography of [Phenyl-UL-$^{13}C_6$/$^{14}C$]BYF 14182 in Male and Female Rats: Distribution of Radioactivity and Elimination from Blood, Organs and Tissues after Single Oral Administration including Determination of Radioactivity in the Excreta and Exhaled $^{14}CO_2$," (J. Koester, Bayer CropScience AG, Development,

Environmental Safety Metabolism/ADME and Environmental Fate, Monheim am Rhein, Germany, Report No. MEF-08/162, 6 April 2009). Eight Wistar Hsd/Cpb: WU rats per sex received a single oral gavage dose of [Phenyl-UL-$^{13}C_6$/$^{14}C$]BYF 14182 at 5 mg/kg. After dosing, one rat per sex was sacrificed at 1, 4, 8, 24, 48 (female only), 72, 120, and 168 hours post-dosing for quantitative whole-body autoradiography (QWBA). Expired air was collected from 3 males and 4 females for 24 and 48 hours post dosing. Urine was sampled at 1, 4, 8, 24, 48, 72, 96, 120, 144, and 168 hours post-dosing. Feces were sampled at 24, 48, 72, 96, 120, 144, and 168 hours post dosing. Approximately 0.06% (males) and 0.009% (females) of radiolabeled dose was exhaled during the 48 hour sampling period respectively. Excretion of radiolabel in feces was 67.50% (males) and 40.96% (females) of dose, while excretion of radiolabel in urine was 33.45% (males) and 59.54% (females) of dose with peak values reached 2 to 3 days post-dosing for both routes. For nearly all organs and tissues, maximum equivalent concentrations ($CEQ_{max}$) (µg a.s.-equiv./g) were reached 1 hour post-dosing ($t_{max}$) for both sexes. Tissue/blood concentration ratios at $t_{max}$ were highest for liver (4.60), kidney (2.87), adrenal gland (1.21), and myocardium (1.05) in males and for liver (3.50), adrenal gland, brown fat, and kidney (all 2.30) in females, while the lowest were for perirenal fat (0.30), vitreal body (0.24), spinal cord (0.15), and brain (0.12) in males and for nasal mucosa (0.47), brain (0.39), and vitreal body (0.28) in females. At day 7, tissue/blood concentrations were highest for liver (0.90), kidney (0.46), lung (0.35), and adrenal gland (0.35) in males and for liver (0.56), lung (0.49), adrenal gland (0.36), kidney (0.35), and nasal mucosa (0.34) in females, while the lowest detectable values were found for thyroid gland (0.18) and skeletal muscle (0.15) in males and for Harderian gland (0.11) and spinal cord (0.10) in females. Supplemental data. (Green, 4/8/13).

53185-0044 267350, "Quantitative Whole Body Autoradiography of [Pyrazole-3-$^{14}C$]BYF 14182 in Male and Female Rats: Distribution of Radioactivity and Elimination from Blood, Organs and Tissues after Single Oral Administration including Determination of Radioactivity in the Excreta and Exhaled $^{14}CO_2$," (J. Koester, Bayer CropScience AG, Development, Environmental Safety Metabolism/ADME and Environmental Fate, Monheim am Rhein, Germany, Report No. MEF-08/179, 30 March 2009). Eight Wistar Hsd/Cpb: WU rats per sex received a single oral gavage dose of [Pyrazole-3-$^{14}C$]BYF 14182 at 5 mg/kg. After dosing, one rat per sex was sacrificed at 1, 4, 8, 24, 48, 72, 120, and 168 hours post-dosing for quantitative whole-body autoradiography (QWBA). Expired air was collected from 4 rats per sex for 24 and 48 hours post dosing. Urine was sampled at 1, 4, 8, 24, 48, 72, 96, 120, 144, and 168 hours post-dosing. Feces were sampled at 24, 48, 72, 96, 120, 144, and 168 hours post dosing. Exhaled radiolabel accounted for 0.054% to 0.069% and 0.045% to 0.051% of dose for males and females respectively during the 48 hour sampling period. Excretion of administered radiolabel in feces accounted for up to 64.61% for males and up to 61.24% for females, while excretion in urine accounted for up to 33.93% for males and up to 57.37% for females with peak values reached 72 to 120 hours (males) and 120 hours (females) post-dosing for both routes. Maximum equivalent concentrations ($CEQ_{max}$) (µg a.s.-equiv./g) in organs and tissues were reached 1 hour post-dosing ($t_{max}$) for both sexes. Tissue/blood concentration ratios at $t_{max}$ were highest for liver (5.37), kidney (2.87), adrenal gland (1.56), Harderian gland (1.07), and myocardium (1.06) in males and for liver (4.40), kidney (2.84), Harderian gland (2.20), brown fat (2.18), and adrenal gland (2.14) in females, while the lowest were for vitreal body (0.20), perirenal fat (0.19), spinal cord (0.12), and brain (0.11) in males and for nasal mucosa (0.51), brain (0.48), and vitreal body (0.33) in females. At day 7, tissue/blood concentrations were highest for liver (0.90), kidney (0.46), adrenal gland (0.35), and lung (0.34) in males and for liver (0.45), lung (0.50), adrenal gland (0.35), kidney (0.33), and nasal mucosa (0.33) in females, while the lowest detectable values were found for thyroid gland (0.27), nasal mucosa (0.18), skeletal muscle and myocardium (both 0.17), and pancreas (0.08) in males and for salivary

gland (0.10), spinal cord (0.10), pancreas (0.08), and brain (0.07) in females. Supplemental data. (Green, 4/9/13).

53185-0044 267356, "[Phenyl-UL-$^{13}C_6$/$^{14}$C]BYF 14182 - Metabolism in Organs and Tissues of Male and Female Rats (3 Time-Points)," (J. Koester, Bayer CropScience AG, Development, Environmental Safety Metabolism/ADME and Environmental Fate, Monheim am Rhein, Germany, Report No. MEF-09/475, August 27, 2009). Three groups of 4 Wistar Hsd/Cpb: WU rats per sex received a single oral gavage dose of [Phenyl-UL-$^{13}C_6$/$^{14}$C]BYF 14182 at 5 mg/kg. Four rats per sex were sacrificed 1, 4, and 24 hours post-dosing. Urine was collected until the scheduled sacrifice times for each group. Additionally, blood (plasma and blood cells), liver, kidney, gastrointestinal tract (GIT) (including feces), skin and carcass were collected from all animals in the group at each scheduled sacrifice. All identified and unknown metabolites were quantitatively determined in composite samples of urine, plasma, and in liver and kidney extracts by HPLC. Group mean recovery of radiolabel accounted for 90.4% to 102.3% (males) and 96.8% to 99.8% (females) of administered dose. 32.3% (males) and 49.2% (females) of the administered radiolabel was excreted in urine through 24 hours post-dosing. The highest mean total radioactive residue (TRR) values in organs, tissues, and combined GIT plus feces were detected 1 hour after dosing for both sexes. At 1 hour post-dosing, group mean TRR values [mg a.s. equiv./$kg_{sample}$] were highest for liver (5.221) followed by kidneys (4.827), plasma (1.467), carcass (0.985), and skin (0853) in males, while values were highest for kidneys (6.352), followed by liver (5.717), skin (1.793), plasma (1.593), and carcass (1.353) in females. At 24 hours post-dosing, group mean TRR values in descending order were liver (0.247), carcass (0.094), kidneys (0.085), plasma (0.029), and skin (0.028) in males and liver (0.291), kidneys (0.130), carcass (0.100), plasma (0.058), and skin (0.055) in females. Metabolic reactions were detected at 10 different structural positions of the test compound. The majority of metabolites was identified (58% to 94% of TRR). Metabolism was qualitatively similar in males and females. Quantitative differences in the amounts of individual metabolites in urine, plasma, liver, and kidney between the sexes were noted. An overview of the principal metabolic reactions of [Phenyl-UL-$^{13}C_6$/$^{14}$C]BYF 14182 in rats along with the schematic of the proposed metabolic pathway were included. Supplemental data. (Green, 4/16/13).

53185-0044 267357, "[Pyrazole-3-14C]BCS-AA10006 (BYF 14182-3-hydroxy-butyl) - Absorption, Distribution, Excretion and Metabolism in the Rat," ( R. Bongartz, Bayer CropScience AG, Development, Environmental Safety, Metabolism/ADME and Environmental Fate, Monheim am Rhein, Germany, Report No. MEF-09/376, August 27, 2009). BYF 14182-3-hydroxy-butyl is a postulated intermediate metabolite in the metabolic pathway of BYF 14182 in rodents. Four male Wistar Unilever Hsd/Cpb: WU rats received a single oral gavage dose of [Pyrazole-3-$^{14}$C]BYF 14182-3-hydroxy-butyl at 2 mg/kg followed by sacrifice 72 hours later. Urine was sampled 4, 8, 12, 24, 48, and 72 hours post-dosing. Feces were sampled 24, 48, and 72 hours after treatment. Plasma was sampled 10, 20, 40, 60, and 90 minutes and 2, 3, 4, 6, 8, 24, 28, 32, 48, 56, and 72 hours after treatment. A mean value of 100.7% of administered radiolabel was recovered in plasma, urine, feces and organs and tissues. The main route of excretion was in the feces with a mean value of 75.27% of dose during 72 hours. Excretion in urine accounted for a mean of 25.04% of dose during 72 hours, and the body including the gastrointestinal tract contained a mean of 0.341% at sacrifice. The mean measured maximum concentration of radiolabel in plasma ( $C_{max}$) was 0.57 µg/g, s22 while the mean measured time to $C_{max}$ ($T_{max}$) was 0.67 hours post-treatment. The plasma concentration curve indicated a fast elimination phase after $C_{max}$. The group mean concentration of radiolabel in plasma at 72 hours was 0.0023 µg/g (0.4% of $C_{max}$). The highest group mean equivalent concentrations of radiolabel were found in liver (0.044 µg/g). Moderate mean equivalent concentrations were found in erythrocytes (~0.039 µg/g) and kidneys (~0.013 µg/g). Radiolabel concentrations were

low (~0.001 to 0.007 µg/g) in the other organs. [Pyrazole-3-$^{14}$C]BYF 14182-3-hydroxy-butyl was extensively metabolized in the rat, and metabolic reactions were observed in the same structural positions as detected for BYF 14182. Metabolites in urine and feces were quantified (radio-HPLC). Parent compound, BYF 14182-3-hydroxy-butyl, was detected in low amounts in urine and feces (0.49% of administered dose for both routes combined). The majority of metabolites, representing ~60% of administered dose, were identified, and other metabolites, representing ~15% of dose, were characterized by extraction and chromatographic behavior. Approximately 17% of the dose was identified as trihydroxy compounds and ~27% as dihydroxy compounds. Oxidation of the hydroxy groups resulted in keto compounds (~25% of the dose) or carboxylic acids (~5% of the dose). An overview of the principal metabolic reactions of [Pyrazole-3-$^{14}$C]BYF 14182-3-hydroxy-butyl in rats along with the schematic of the proposed metabolic pathway were included. Supplemental data. (Green, 4/17/13).

## GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT

### Acute oral toxicity, rat

**53185-0031 267288, "BYF 14182, Acute Toxicity in the Rat after Oral Administration", (M. Schüngel, Bayer HealthCare AG, PH-GDD Toxicology, Wuppertal, Germany, Study No. T 3077694, 30 July 2007). Three female HsdCpb:Wu Wistar rats received a single oral gavage dose of BYF 14182 (penflufen technical) (95.6%) at 2000 mg/kg followed by a 14 day observation period. The dosing regimen was subsequently repeated with another group of 3 females. No clinical signs were observed. All animals survived through the 14 day observation period and gained bodyweight. Necropsy results were unremarkable. $LD_{50}$ ≥ 5000. Toxicity category IV. Acceptable. (Green, 11/19/12)

### Acute dermal toxicity

**53185-0031 267289, "BYF 14182, Acute Toxicity in the Rat After Dermal Application", (M. Schüngel, Bayer HealthCare AG, BSP-GDD-GED General Toxicology, Wuppertal, Germany, Study No. T 4077695, August 31, 2007). Five HsdCpb:Wu Wistar rats per sex received a single 24 hour dermal exposure (clipped, unabraded, occluded skin) to BYF 14182 (penflufen technical) (95.6%) at 2000 mg/kg followed by a 14 day observation period. No treatment-related clinical signs, dermal irritation, bodyweight changes, or necropsy findings were indicated. $LD_{50}$ (male and female) > 2000 mg/kg. Toxicity category III. Acceptable. (Green, 11/20/12).

### Acute inhalation toxicity, rat

**53185-0031 267290, "BYF 14182, Acute Inhalation Toxicity in Rats", (A. Folkerts, Bayer HealthCare AG, BSP-GDD TOX-GT Inhalation Tox., Wuppertal, Germany, Study No. T 5077696, original date: 7 December 2007, Final revision: 30 January 2008). Five HsdCpb:Wu Wistar rats per sex were exposed to BYF 14182 (technical penflufen) (95.6%) for 4 hours by nose-only inhalation at 2.02 mg/l gravimetric (with a mass median aerodynamic diameter (MMAD) of 3.83 and 4.38 µm and a geometric standard deviation (GSD) of 1.70 and 1.64, respectively) followed by a 14 day observation period. A vehicle control group (5 per sex) received untreated air. All vehicle control and treated animals survived to the end of the 14 day observation period and gained bodyweight. Up to 4 per sex treated animals showed piloerection, bradypnea, labored breathing patterns, dyspnea, breathing sounds, reduced motility, limping, high legged gait, staggering gait, and/or red encrusted nose that lasted up to post-exposure day 3. Rectal temperatures of treated animals were significantly reduced compared to vehicle control animals. No treatment-related necropsy results. $LC_{50}$ (males and females) > 2.02 mg/l. Toxicity category IV. Acceptable. (Green, 11/26/12).

### Primary eye irritation, rabbit

**53185-0031 267291, "BYF 14182, Acute Eye Irritation on Rabbits", ( C. Gmelin, Bayer HealthCare AG, BSP-GDD-GED General Toxicology, Wuppertal, Germany, Study No. T 5077579, 10 October 2007). 100 mg of BYF 14182 (penflufen technical) (95.6%) was placed into the lower conjunctival sac of one eye of each of three female albino Crl:KBL(NZW)BR rabbits followed by a 72 hour observation period. Treated eyes were rinsed with 0.9% saline 24 hours after application. Untreated eyes served as controls. The following eye effects were recorded: iritis (score of 1) in the treated eye of 1 animal at 1 hour post application (p.a.); chemosis of the conjunctivae (scores of 1) in treated eyes of all animals at 1 hour p.a., persisting in 1 animal at 24 hours p.a.; and redness of the conjunctivae (scores of 2) in all animals at 1 hour p.a, persisting in 2 animals at 24 hours p.a. (both had scores of 0 at 48 hours) and evident as a score of 1 in one animal at 24 and 48 hours p.a. All eyes were clear at 72 hours. Corneal involvement was not indicated. Toxicity category III. Acceptable. (Green, 11/27/12).

### Primary dermal irritation

**53185-0031 267292, "BYF 14182, Acute Skin Irritation/Corrosion on Rabbits", ( C. Gmelin, Bayer HealthCare AG, BSP-GDD-GED General Toxicology, Wuppertal, Germany, Study No. T 3077577, October 2, 2007). Three female albino Crl:KBL(NZW)BR New Zealand rabbits received a single 4-hour exposure (clipped, unabraded, semi-occluded skin) to BYF 14182 (penflufen technical) (95.6%) at 500 mg followed by a 72-hour observation period. No dermal irritation was indicated through 72 hours post patch removal. Erythema, eschar, and edema scores were 0 at all times points. Toxicity category IV. Acceptable. (Green, 11/29/12).

### Dermal sensitization

**53185-0031 267293, 267294, "BYF 14182, Study for the Skin Sensitization Effect in Guinea Pigs (Guinea Pig Maximization Test According to Magnusson and Kligman)", H. W. Vohr, Bayer HealthCare AG, PH-GDD Toxicology, Wuppertal, Germany, Study No. T 4077325, 12 July 2007 (amended 10 August 2007)). Thirty female Crl: HA guinea pigs (20 test group and 10 control animals) were used. Polyethylene glycol 400 (PEG) was used as vehicle. For intradermal induction, test group animals received the following pairs of injections: (1) complete Freund's adjuvant (FCA) diluted 1:1 with sterile physiological saline; (2) 2.5% BYF 14182 (penflufen technical) (95.6%) formulated in polyethylene glycol 400 (PEG); and (3) 2.5% BYF 14182 formulated in equal parts PEG and FCA. Intradermal induction control group animals received the same pair of injections at site one; 100% PEG at site 2; and a 1:1 mixture of PEG and FCA at site 3. At topical induction (48 hours), performed 1 week after intradermal induction, test group animals received a patch with 0.5 ml of 50% BYF 14182 in PEG and control group females were treated with 0.5 ml of 100% PEG. At topical challenge (24 hours), performed 2 weeks after topical induction, test and control group animals received one patch with 50% test article in PEG and another with 100% PEG (the topical challenge was repeated 1 week later). The first topical challenge resulted in 5/20 animals (25%) with skin reaction scores of grade 1. Control group animals showed no skin effects (scores of 0). After the repeat challenge, 2/20 test group animals (10%) showed skin reaction scores of 1. Control group animals all had scores of 0. BYF 14182 was not a dermal sensitizer in the Magnusson-Kligman guinea pig maximization test. Method validation (record 267294) was included. Acceptable. (Green, 12/3/12).

## SUBCHRONIC STUDIES

### Rat 28-Day Dietary Toxicity Study

53185-0046 267359, "BYF 14182, Exploratory 28-Day Toxicity Study in the Rat by Dietary Administration", (G. Steiblen, Bayer CropScience, Sophia Antipolis, France, Study No. SA 03339, July 22, 2004). Five Wistar Rj: WI (IOPS HAN) rats per sex per group received BYF 14182 (penflufen technical) (99.2% to 99.4%) in the diet for 28 days at 0 (basal diet), 150, 2000, and 7000 ppm (mean achieved levels of 12, 154, and 560 mg/kg/day in males and 13, 169, and 648 mg/kg/day in females, respectively). No mortality and no treatment-related clinical signs were observed during the study. Reductions in group mean bodyweight (3% to 7% (ns)) and bodyweight gain (12%, statistical significance at day 15 only) were noted for high dose females vs controls. Mid dose females showed a 9% reduction (ns) in bodyweight gain compared with controls during 28 days. Bodyweight and bodyweight gain for treated males were comparable to controls during the study period. Group mean food consumption was reduced for high dose females throughout the treatment period (9% (ns)) compared to controls. In mid dose females, food consumption was comparable to controls for study days 1 to 8 and significantly reduced (9%) thereafter. Male food consumption at all dose levels was comparable to controls throughout the study. Significantly higher mean erythrocyte counts, associated with lower mean reticulocyte counts, were noted for females at the mid and high dose levels vs controls. Statistically significant clinical chemistry variations (relative to controls) noted in females included reduced mean total bilirubin concentration and mean aspartate aminotransferase activity at the high dose level, and increased mean total protein (high dose) and mean total cholesterol concentrations (mid and high dose). Male clinical chemistry values were comparable to controls across all test groups. Group mean relative liver weights were significantly increased for mid and high dose males and for high dose females vs controls. At terminal necropsy, 4/5 males and 2/5 females at 7000 ppm had enlarged livers. Histology indicated an increase in minimal (3/5 males and 5/5 females) to slight (2/5 males) hypertrophy of centrilobular hepatocytes in liver at the high dose and in 2/5 mid dose males (minimal severity) vs controls. In kidneys, an increase in the severity of intraepithelial hyaline droplets in the proximal convoluted tubules was noted for high dose males. Additionally, group mean total cytochrome P-450 in liver was significantly increased in both sexes at the high dose level and slight to moderate increases in group mean benzoxyresorufin o-debenzylation (BROD) and pentoxyresorufin o-depentylation (PROD) activities were noted for both sexes at 2000 and 7000 ppm vs controls. NOEL = 150 ppm (12 mg/kg/day for males and 13 mg/kg/day for females) based on liver weights and enzyme parameters. No adverse effect. Supplemental data. (Green, 12/18/12) (no worksheet)

### Rat 90-Day Oral (Feeding) Toxicity Study

**53185-0032, 0046 267295, 267296, 267359, "BYF 14182, 90-Day Toxicity Study in the Rat by Dietary Administration", (G. Steiblen, Bayer CropScience, Sophia Antipolis, France, Study No. SA 04199, June 16, 2006). Ten Wistar Rj: WI (IOPS HAN) rats per sex per group received BYF 14182 (penflufen technical) (98.8%) in the diet at 0 (basal diet), 150, 7000, and 14000 ppm for 90 days. Group mean achieved dosages were 9.5, 457, and 949 mg/kg/day for males and 11.4, 492, and 1009 mg/kg/day for females at 150, 7000, and 14000 ppm, respectively. At 14000 ppm, group mean bodyweight gain for males was significantly reduced (22%) during the first week of the study vs controls, and was comparable to controls thereafter. Group mean bodyweight gain and food consumption for females was significantly reduced at the mid and high dose levels vs controls for most time points during the study. Group mean absolute and relative liver weights were significantly increased in both sexes at the mid and high dose levels relative to controls. At terminal sacrifice, enlarged livers were noted for all high dose animals and for 8/10 males and 7/10 females at 7000 ppm. Treatment-related histology was noted in

liver, kidney, thyroid gland, and pituitary gland. In liver, centrilobular hepatocellular hypertrophy (minimal to moderate) was noted at the mid dose (all animals) and high dose levels (9/10 males, all females). In kidney, an increased incidence of tubular hyaline droplets was recorded for males at 7000 ppm (5/10) and 14000 ppm (6/10) vs controls (2/10). Thyroid gland changes included increased diffuse follicular cell hypertrophy (minimal to slight) at the mid dose (8/10 males) and high dose level (8/10 males and 6/10 females) and increased focal/multifocal colloid alteration (minimal to slight) in males at 7000 ppm (3/10) and 14000 ppm (3/10) vs controls. Increased slight to minimal focal/multifocal basophil cell hypertrophy was noted in the pituitary gland of mid dose (6/10) and high dose (5/10) males. Record 267296 is a supplemental 90 dietary toxicity study in rats. Record 267359 is an exploratory/dose-ranging 28-day dietary toxicity study in rats. NOEL = 150 ppm (9.5 mg/kg/day (males) and 11.4 mg/kg/day (females)) based on liver weights and liver macroscopy and histology. No adverse effect. Acceptable. (Green, 12/20/12).

53185-0032 267296, "BYF 14182, 90-Day Toxicity Study in the Rat by Dietary Administration - Complementary Study-", (G. Steiblen, Bayer CropScience, Sophia Antipolis, France, Study No. SA 05148, 19 June 2006). Ten Wistar Rj: WI (IOPS HAN) rats per sex per group received BYF 14182 (penflufen technical) (≥ 98.2%) in the diet at 0 (basal diet), 50, 150, and 3500 ppm for 90 days. Group mean achieved dosages were 3.2, 9.3, and 228 mg/kg/day for males and 3.7, 11.4, and 260 mg/kg/day for females at 50, 150, 3500 ppm, respectively. One high dose male was sacrificed for humane reasons (reduced motor activity, noisy respiration) on study day 69. No treatment-related clinical signs were noted for surviving animals during the study. Significant reductions were noted in group mean bodyweight for days 43, 50, 57, and 64 and in bodyweight gain for days 29, 50, and 57 for high dose females vs controls. Terminal bodyweights were also significantly reduced for high dose females vs controls. Group mean food consumption for females at 3500 ppm was significantly reduced for days 15, 29, 36, 43, 50, 57, and 64 compared to controls. Group mean absolute and relative liver weights were significantly increased for both sexes at 3500 ppm vs controls. Treatment-related necropsy results included an increase in enlarged liver in high dose females (4/10) vs controls (0/10). Treatment-related histology included increased minimal diffuse centrilobular hepatocellular hypertrophy in liver of 2/9 males and 5/10 females and the presence of focal/multifocal hyaline droplets in kidneys of 3/9 males at the high dose level vs controls (0 incidence in controls for both findings). NOEL = 150 ppm (9.3 mg/kg/day (males) and 11.4 mg/kg/day (females)) based on liver weight and liver histology. No adverse effect. Supplemental data. (Green, 12/20/12). No worksheet.

### Mouse 28-Day Dietary Toxicity Study

53185-0046 267360, "BYF 14182, Preliminary 28-Day Toxicity Study in the Mouse by Dietary Administration", (J.B. Rascle, Bayer CropScience, Sophia Antipolis, France, Study No. SA 04191, June 24, 2005). Five C57BL/6J mice per sex per group received BYF 14182 (penflufen technical) (98.6%) in the diet at 0 (basal diet), 150, 3500, and 7000 ppm for 28 days. Group mean achieved dose levels were 26, 632, and 1274 mg/kg/day for males and 31, 741, and 1585 mg/kg/day for females at 150, 3500, and 7000 ppm, respectively. No mortality and no treatment-related clinical signs were recorded. Group mean bodyweight for mid and high dose females was reduced (3% to 7%, ns) for study days 8, 15, and 22 compared to controls. Group mean food consumption for both sexes at all treated levels was comparable to controls. Significant reductions were noted for group mean total cholesterol (both sexes at 3500 and 7000 ppm) and total protein (mid and high dose females) vs controls. Group mean alkaline phosphatase activity was significantly increased for high dose females vs controls. Group mean relative liver weights were significantly increased for both sexes at 3500 and 7000 ppm vs controls. At 7000 ppm, enlarged liver was noted for 4/5 males and 2/5 females. Treatment-

related histology was noted in liver: minimum diffuse centrilobular hepatocellular hypertrophy was observed in 1/5 males and 3/5 females at 7000 ppm. NOEL = 150 ppm (26 mg/kg/day for males and 31 mg/kg/day for females) based on liver weight. No adverse effect. Supplemental data. (Green, 12/27/12). No worksheet.

### Mouse 90-Day Dietary Toxicity Study

53185-0033, 0046 267297, 267360, "BYF 14182, 90-Day Toxicity Study in the Mouse by Dietary Administration", (G. Steiblen, Bayer CropScience, Sophia Antipolis, France, Study No. SA 05029, January 6, 2006). Ten C57BL/6J mice per sex per group received BYF 14182 (penflufen technical) (98.8%) in the diet at 0 (basal diet), 150, 3500, and 7000 ppm for 90 days. Group mean achieved dosages were 26.9, 638, and 1238 mg/kg/day for males and 31.5, 757, and 1600 mg/kg/day for females at 150, 3500, and 7000 ppm, respectively. There were no mortalities. Significant reductions in group mean total cholesterol (both sexes at the mid and high dose levels) and total protein (high dose females) were noted vs controls. Group mean relative liver weights were significantly increased for both sexes at 3500 and 7000 ppm vs controls. Gross pathology indicated enlarged livers for 5/10 males and 1/10 females at the mid dose and 9/10 males and 8/10 females at the high dose level. Histopathology revealed minimal to mild diffuse centrilobular hepatocellular hypertrophy in liver of mid (4/10 males and 4/10 females) and high dose animals (9/10 males and 7/10 females). Record 267360 is a preliminary 28-day dietary toxicity study in mice. NOEL = 150 ppm (26.9 mg/kg/day (males) and 31.5 mg/kg/day (females)) based on liver weights and liver histology. No adverse effect. Supplemental data (no hematology or ophthalmology, incomplete clinical chemistry and gross pathology) . (Green, 1/2/13).

### Dog 28-Day Dietary Toxicity Study

53185-0046 267361, "BYF 14182, Preliminary 28-Day Toxicity Study in the Dog by Dietary Administration", ( A. McElligott, Bayer CropScience, Sophia Antipolis, France, Study No. SA 04300, August 30. 2005). Two Beagle dogs per sex per group received BYF 14182 (penflufen technical) (98.8%) in the diet at 0 (basal diet), 1300, 6500, and 26000 ppm for 28 days. All dogs survived to terminal sacrifice. Group mean achieved dosages were 49, 244, and 759 mg/kg/day for males and 52, 246, and 895 mg/kg/day for females at 1300, 5600, and 26000 ppm, respectively. No treatment-related changes were noted for clinical signs, ophthalmology, hematology, urinalysis, or gross pathology at any dose level. At the high dose level, bodyweight was reduced 0.1 and 0.3 kg in the 2 males, respectively, vs a gain of 0.1 kg and a loss of 0.1 kg for male controls and 1 female showed a 0.2 kg loss vs a slight gain in the 2 female controls for study days 1 to 8. At the mid dose, bodyweight decreases of 0.2 kg in 1 male and 0.1 kg in 1 female were noted compared to controls for study days 1 to 8. Bodyweight progression was comparable to controls at both dose levels for the remainder of the study. Food consumption was slightly lower at 26000 ppm in 2 males and 1 female for study day 1 to 8 vs controls and continued in the female and 1 male during the 28 day treatment period. At 6500 ppm, food consumption was marginally lower for 1 per sex during study days 1 to 8 and comparable to controls for the remainder of the treatment period. At 26000 ppm, clinical chemistry changes included: increased alkaline phosphatase activity for all animals relative to their pre-exposure values (+63% and +113% in males and +61% and +116% in females); a tendency towards higher gamma glutamyltransferase activity in males (3 times the pretest value); decreased total cholesterol in 1 male (-35%) and both females (-36% and -34%) vs pretest values; and decreased albumin in 1 male (-16%) and both females (-16% and -18%) vs pretest data. Alkaline phosphatase activity was increased at 6500 ppm in 1 male (+116%) and 1 female (+127%) vs pretest numbers. Absolute and relative liver weights were increased for both sexes at 6500 and 26000 ppm vs controls. Slight to moderate diffuse centrilobular hepatocellular hypertrophy was noted in liver for all high dose animals and at minimum severity for both males

and 1 female at the mid dose level. In thyroid gland, decreased minimal to moderate diffuse follicular diameter was noted in all high dose males and females and in both males and 1 female at 6500 ppm. NOEL = 1300 ppm ( 49 mg/kg/day for males and 52 mg/kg/day for females) based on liver weight, liver and thyroid gland histology, and clinical chemistry. No adverse effect. Supplemental data. (Green, 1/4/13). No worksheet.

### Dog 90-Day Oral (Dietary) Toxicity Study

**53185-0033, 046 267298, 267361, "BYF 14182, 90-Day Toxicity Study in the Dog by Dietary Administration", (P. Kennel, Bayer CropScience, Sophia Antipolis, France, Study No. SA 06327, February 29, 2008). Four Beagle dogs per sex per group received BYF 14182 (penflufen technical) (95.6%) in the diet at 0 (basal diet), 180, 1800, and 18000 ppm for 13 weeks. Group mean achieved dosages were 5.6, 55.7, and 532 mg/kg/day for males and 6.1, 63.1, 568 mg/kg/day for females at 180, 1800, and 18000 ppm, respectively. All animals survived to terminal necropsy. No treatment-related changes were noted for clinical signs, physical examinations, ophthalmology, urinalysis, or gross pathology. Group mean bodyweight gains for females at 18000 ppm were significantly reduced for study days 15 through 91 compared to controls. Group mean food consumption was reduced at 18000 ppm for males (39%) and females (35%) compared to controls (ns) during week 1 and, overall during weeks 1 through 13, for males (8%) and females (21%, with statistical significance at weeks 7 and 11) vs controls. Group mean platelet counts were significantly increased for high dose females at weeks 12-13 relative to controls. At 18000 ppm, group mean alkaline phosphatase activity was significantly increased for both sexes at weeks 7 and 12-13 and total cholesterol was significantly decreased for males at week 12-13 vs controls. Group mean relative liver weights were significantly increased for both sexes at 18000 ppm compared to controls. Also, group mean liver to brain weight was significantly increased for mid dose males. Group mean adrenal gland absolute and brain weight ratios were significantly increased for high dose males vs controls. In liver, at 18000 ppm, minimal to slight diffuse panlobular hepatocellular hypertrophy was noted in all males and females along with minimal multifocal intrahepatocellular eosinophilic material in 2 males and 1 female, and minimal multifocal perilobular single cell death in 2 males and 1 female. Additionally, at the mid dose, minimal diffuse panlobular hepatocellular hypertrophy was noted in the liver of 1 males and 3 females. In adrenal gland, slight diffuse cortical hypertrophy/hyperplasia was noted in 2 high dose males. Record 267361 is a preliminary 28-day dietary toxicity study in dogs used to set dosing levels. NOEL = 180 ppm (5.6 mg/kg/day for males and 6.1 mg/kg/day for females) based liver histology. No adverse effect. Acceptable. (Green, 1/7/13).

### Rat 4-Week Dermal Toxicity Study

**53185-0034 267299, "A Subacute Dermal Toxicity Study in Rats with BYF 14182", (L.P. Sheets, Bayer CropScience LP, Stilwell, KS, Report No. 202021, July 22, 2009). Ten Wistar Hanover IGS [CRL:WI(Han)] rats per sex per group were dermally treated (clipped, unabraded, semi-occluded) with BYF 14182 (penflufen technical) (95.6%) at 0 (deionized water), 100, 300, and 1000 mg/kg/day for 4 weeks (6 hours per day, 5 days per week). One 300 mg/kg/day male died on study day 10. The death was considered incidental and likely due to the dosing procedure (too tight elastic bandage). No treatment-related changes were noted for clinical signs, bodyweight, food consumption, ophthalmology, hematology, clinical chemistry, or gross pathology at any treatment level. Histology results included significant increases in lymphocyte debris within the thymic cortices (minimal severity) of both sexes at 1000 mg/kg/day. Systemic NOEL = 300 mg/kg/day (males and females) based on thymus histopathology. No adverse effect. Acceptable. (Green, 1/8/13).

## CHRONIC STUDIES

### Chronic, rat

****53185-0032, 0039 267296, 267305**, "Chronic Toxicity and Carcinogenicity Study of BYF 14182 in the Wistar Rat by Dietary Administration," (J.B. Rascle, Bayer CropScience, Sophia Antipolis, France, Study No. SA 06115, November 27, 2009). In the carcinogenicity phase, sixty Wistar Rj:WI (IOPS HAN) rats per sex per group received BYF 14182 (penflufen technical) (95.6%) in the diet at 0 (basal diet), 100, 2000, and 7000 ppm for 104 weeks. Ten per sex per group interim sacrifice animals received the same treatment regimen for 52 weeks followed by necropsy. For the reversibility phase, 10 per sex per group received the same treatment regimen for 52 weeks followed by a 13-week period receiving untreated diet followed by necropsy. Group mean achieved dietary intake during treatment weeks 1 to 104 was 4.0, 79, and 288 mg/kg/day for males and 5.6, 113, and 399 mg/kg/day for females at 100, 2000, and 7000 ppm respectively. No treatment-related effects were indicated for clinical signs, mortality, ophthalmology, or hematology. At 7000 ppm, group mean bodyweight was significantly reduced at most time points for males (↓3% to ↓9% from treatment week 5) and females (↓7% to ↓17% from treatment day 8) through treatment week 102 vs controls. Group mean food consumption at the high dose level was reduced for males from study week 4 to the end of the treatment period (↓7% or less with statistical significance occasionally) vs controls. High dose female group mean food consumption was reduced from study week 11 onwards as much as 5% with statistical significance on some occasions during the first year and up to 17% with statistical significance on most occasions during the second year vs controls. At 2000 ppm, from week 21 onwards, group mean food consumption for females was reduced as much as 5% during the first year and up to 17% during the second year of the study (with statistical significance on some occasions) vs controls. Group mean food consumption for mid dose males was comparable to controls during the study. Group mean total bilirubin concentrations were significantly reduced (on most occasions) for males and females at 2000 ppm and 7000 ppm during the treatment period. The reductions were completely reversed for females and partially so for males at the high dose level during the recovery phase. At the 12- and 24-month sacrifices, group mean relative liver weights (% bodyweight) were significantly increased in both sexes at 7000 ppm and in females at 2000 ppm vs controls (recovery phase values were comparable to controls at all dose levels). Increased incidences of enlarged liver and dark liver were noted for both sexes at 7000 ppm vs controls at the 12-month sacrifice. At the high dose level, 12-month sacrifice liver histology (scheduled and unscheduled deaths) included increased minimal to slight centrilobular to panlobular hepatocellular hypertrophy in both sexes, centrilobular diffuse hepatocellular macrovacuolation in both sexes, and focal hepatocellular brown pigment in females. Also, at 12-months, thyroid gland histology at 7000 ppm included increases in minimal diffuse follicular cell hypertrophy in both sexes and in minimal to slight colloid alteration in females vs controls. No treatment-related neoplastic findings were noted for 12-month sacrifice animals. At the 24-month sacrifice, an increase in dark liver, enlarged liver, and white focus in the liver was noted for high-dose females; the latter 2 changes were also increased for mid-dose females vs controls. 24-month carcinogenicity phase non-neoplastic histopathology (scheduled and unscheduled deaths) at the mid- and high-dose levels included significant increases in centrilobular to panlobular hepatocellular hypertrophy (minimal, slight, moderate) in liver of both sexes (also noted in low-dose males), in diffuse centrilobular hepatocellular macrovacuolation (minimal to marked) in liver of both sexes, in focal hepatocellular brown pigment (minimal, slight) in liver of females, in eosinophilic focus(I) of hepatocellular alteration (minimal to moderate) in liver of females, and in thyroid gland colloid alteration (minimal to moderate) in females (and high dose males) vs controls. Neoplastic findings for 24-month carcinogenicity phase animals included significant increases (both for trend and for pair wise comparisons) in the liver of females at 2000 ppm in incidental

hepatocellular adenomas (5/60) vs controls (0/60) and in hepatocellular carcinomas plus adenomas (6/60) vs controls (0/60). At 7000 ppm, the incidence of incidental hepatocellular adenoma (4/60) and hepatocellular carcinoma plus adenoma (4/60) in liver of females was slightly increased (ns) vs controls. In hematopoietic tissue, the incidence of malignant histiocytic sarcoma was significantly increased (both for trend and for pair wise comparisons) for high dose males vs controls. Record 267296 is a supplemental 90 dietary toxicity study in rats. Chronic NOAEL = 100 ppm (4.0 mg/kg/day for males and 5.6 mg/kg/day for females) based on liver histology, reduced total bilirubin. **Possible adverse effects** include increased hepatocellular adenomas and hepatocellular carcinomas plus adenomas in liver of females, and increased malignant histiocytic sarcomas in hematopoietic tissue of males. Acceptable. (Green and Leung, 1/29/13).

### Chronic, dog

**53185-0037 267303, "BYF 14182, Chronic Toxicity in the Dog by Dietary Administration." (P. Kennel, Bayer CropScience, Sophia Antipolis, France, Study No. SA 06328, June 19, 2009). Four Beagle dogs per sex per group received BYF 14182 (penflufen technical) (95.6%) in the diet at 0 (basal diet), 200, 1000, and 10000 ppm for 52 weeks. Group mean achieved dosages for weeks 1 to 52 were 6.8, 32.0, and 357 mg/kg/day for males and 7.7, 37.9, and 425 mg/kg/day for females at 200, 1000, and 10000 ppm respectively. At the high dose level, overall group mean bodyweight gain for females at the end of the treatment period was reduced 54% vs controls (ns) (1.2 kg vs 2.6 kg), and day 364 group mean bodyweight for females was reduced 18% vs controls (ns) (6.9 kg vs 8.9). Group mean bodyweight and bodyweight gain for high dose males were generally comparable to controls. Group mean food consumption at 10000 ppm was reduced 33% in males ($p \leq 0.05$) and 21% in females (ns) vs controls during the first week of treatment. Values for both sexes at 10000 ppm were comparable to controls for treatment weeks 1 to 52 (92% (males) and 102% (females) of control values). Group mean alkaline phosphatase activity at 10000 ppm was increased for both sexes at months 4, 7, and 12 compared with controls (statistically significant at all 3 time points for females and at month 4 for males). Decreased group mean values were noted for albumin (statistically significant (ss) at months 4 and 12 for both sexes also at month 7 for females), calcium (ss at month 4 in males and month 12 in females), and for inorganic phosphorus (ss at month 12 in males) at 10000 ppm compared with controls. At 10000 ppm, group mean relative liver weights (% of control) were increased in both sexes (with statistical significance in females only). Also at the high dose level, an enlarged liver was noted in 1 male, and dark thyroid glands were recorded for 1 per sex. At 10000 ppm, histology results included increased panlobular hepatocellular hypertrophy (minimal to slight) in liver of 3 males and 4 females (also in 1 mid dose female), reduced diffuse hepatocellular glycogen accumulation (minimal to slight) in liver of both sexes, increased focal hepatocellular brown pigment (minimal) in liver of 2 males (also in 1 mid dose male) and 3 females, and increased diffuse follicular cell hypertrophy (minimal to slight) in thyroid gland of 1 male and 3 females vs controls. Chronic NOAEL = 1000 ppm (32.0 mg/kg/day in males and 37.9 mg/kg/day in females) based on liver and thyroid gland histology and clinical chemistry. No adverse effect. Acceptable. (Green and Leung, 2/6/13).

### Oncogenicity, rat

See Chronic, rat above.

### Oncogenicity, mouse

**53185-0033, 0038 267297, 267304, "Carcinogenicity Study of BYF 14182 in the C57BL/6J Mouse by Dietary Administration," (M. Odin-Feurtet, Bayer CropScience, Sophia Antipolis, France, Study No. SA 06326, October 23, 2009). Fifty C57BL/6J mice per sex per group received BYF 14182 in the diet at 0 (basal diet), 100, 1000, and 6000 ppm for 78 weeks. An

additional 10 per sex per group interim sacrifice animals received the same treatment regimen for 52 weeks followed by necropsy. Group mean achieved dietary intake during treatment weeks 1 to 80 was 14.3, 146, and 880 mg/kg/day for males and 18.4, 182, and 1101 mg/kg/day for females at 100, 1000, and 6000 ppm respectively. No treatment-related effects were noted for clinical signs or mortality. Group mean cumulative bodyweight gain was significantly reduced at 6000 ppm on treatment days 8, 15, 43, 64, 85, 120, and 316 for females and on days 43, 344, and 372 for males vs controls. Group mean bodyweights for both sexes were generally comparable to controls during the study. Significant increases were noted in group mean values for mean corpuscular volume (months 13 and 19 in males), mean corpuscular hemoglobin (month 13 (males) and 19 (both sexes)), and mean corpuscular hemoglobin concentration (month 19 (both sexes)) at 6000 ppm vs controls. Additionally, at 1000 ppm, group mean corpuscular hemoglobin concentration was significantly increased at month 19 for males vs controls. At 6000 ppm, significant increases were noted for group mean relative liver weights (% bodyweight) at the 12-month interim sacrifice in both sexes (absolute weights were also increased for males) and for group mean absolute and relative liver weights at the 18-month terminal sacrifice in both sexes vs controls. At the 18-month sacrifice, the incidence of enlarged liver was increased for high dose males (2/45) vs controls (0/35) and for mid (15/46) and high dose females (33/45) vs controls (5/44). Additionally, enlarged thyroid was increased for high dose females (9/45) at the 18 month sacrifice vs controls (1/44). Non-neoplastic lesions noted for the oncogenicity phase animals (scheduled and unscheduled deaths combined) included significant increases in diffuse centrilobular hepatocellular hypertrophy (minimal, slight, moderate) in liver of mid and high dose males and females (and in low dose males), in diffuse hepatocellular vacuolation (minimal to moderate) in liver of high dose males, in periportal diffuse hepatocellular macrovacuolation in liver of high dose females, and in focal/multifocal follicular cell hyperplasia (minimal to marked) in thyroid gland of high dose females compared to control values. Chronic NOAEL = 1000 ppm (146 mg/kg/day (males) and 182 mg/kg/day (females)) based on liver weight and liver histology. Carcinogenicity NOEL = 6000 ppm (880 mg/kg/day (males) and 1101 mg/kg/day (females)). No adverse effect. Acceptable. (Green and Leung, 2/4/13).

## GENOTOXICITY

### Gene mutation

**53185-0040 267306, "BYF 14182, Salmonella/Microsome Test, Plate incorporation and Preincubation Method," (B. Herbold, Bayer HealthCare AG, BSP-GDD-GED-GTOX Genetic Toxicology, Wuppertal, Germany, Study No. T 8077202, 22 November 2007). Triplicate cultures of *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were exposed to BYF 14182 (penflufen technical) (95.6%), in the presence and absence of rat liver S9 mix, at 0 (DMSO), 16, 50, 158, 500, 1581, and 5000 $\mu$g/plate for 48 hours (at 37°C) after plate incorporation. In a second trial at the same treatment levels, cultures were preincubated for 20 minutes prior to plating. Precipitation was noted at 500 $\mu$g/plate (strains TA 100, TA 1535, TA 1537) and at 1581 and 5000 $\mu$g/plate (all strains) in the presence and absence of activation. Reduced background lawn and/or bacteriotoxic effect was reported at 1581 and 5000 $\mu$g/plate with and without S9 mix. There were no increases in the number of revertants per plate compared to the solvent controls. Positive controls were functional. No adverse effect. Acceptable. (Green and Leung, 3/4/13).

**53185-0040 267307, "Salmonella Typhimurium Reverse Mutation Assay with BYF 14182," (A. Sokolowski, Harlan, Cytotest Cell Research GmbH (Harlan CCR), Rossdorf, Germany, Study Number 1271801, 24 August 2009). Triplicate cultures of *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were exposed to BYF 14182 (penflufen

technical) (94.4%), in the presence and absence of rat liver S9 mix, at 0 (untreated), 0 (DMSO), 3, 10, 33, 100, 333, 1000, 2500, and 5000 µg/plate for 48 hours (at 37°C) after plate incorporation. In a second trial at the same treatment levels, cultures were preincubated for 60 minutes prior to plating. Cultures at all treatment levels, with and without S9 mix, showed normal background lawn growth. A slight reduction in the number of revertants was noted in strain TA1537 at 2500 and 5000 ug/plate under non-activated conditions in trial 1. Test article precipitation in the test tubes and on the incubated agar plates was noted at 1000, 2500, and 5000 µg/plate, with and without activation, in both trials. There were no increases in the number of revertants per plate compared to the solvent controls. Positive controls were functional. No adverse effect. Acceptable. (Green and Leung, 3/5/13).

**53185-0040 267310, "BYF 14182, V79/HPRT-Test *In Vitro* for the Detection of Induced Forward Mutations," (G. Entian, Bayer Health/Care AG, GDD-GED General Toxicology, Wuppertal, Germany, Study No. T 1080085, June 8, 2009). Exponentially growing V79 cells (4 x $10^6$) were plated (75 $cm^2$ flasks) in duplicate and treated with BYF 14182 (penflufen technical) (95.6%) for 5 hours at untreated, 0 (DMSO), 12.5, 25, 50, 75, 100, 125, 150, and 175 µg/ml in the absence of rat liver S9 mix and at untreated, 0, 50, 75, 100, 125, 150, 175, and 200 µg/ml in the presence of S9. Two trials were performed. Complete cytotoxicity was noted at 125 µg/ml and higher in the absence of S9 mix in both trials and at 175 µg/ml and higher in the first trial and at 150 µg/ml and higher in the second trial with S9. No increase in the forward gene mutation frequency. Acceptable. (Green and Leung, 3/8/13).

**53185-0040 267311, "Gene Mutation Assay in Chinese Hamster V79 Cells *In Vitro* (V79/HPRT) with BYF 14182," (H.E. Wollny, Harlan Cytotest Cell Research GmbH (Harlan CCR) Rossdorf, Germany, Study No. 1271802, October 28, 2009). V79 cells at 1.5 x $10^6$ per plastic culture flask were exposed in duplicate to BYF 14182 (penflufen technical) (94.4%) for 4 hours at 0 (tetrahydrofuran (THF)), 2.3, 4.5, 9, 18, 27, 36, 45, and 54 µg/ml in the absence of S9 mix and at 0 (THF), 4.7, 9.4, 18.8, 37.5, 75, 100, 125, and 150 µg/ml with S9. Two trials were performed. Precipitation was noted at 75, 100, 125, and 150 µg/ml with S9 mix. Severe cytotoxicity (relative cloning efficiency of 0% to 2.3%) was noted at 45 and 54 µg/ml in the absence of S9 mix and at 150 µg/ml with S9. At 36 µg/ml, relative cloning efficiency was strongly reduced in both non-activated cultures in the first trial (values were 8.9% and 15.4%) and in one culture in the second trial (the value was 13.6%). Positive controls were functional. There was no increase in the frequency of forward gene mutations. Acceptable. (Green and Leung, 3/12/13).

### Chromosome damage

**53185-0040 267314, "BYF 14182, *In Vitro* Chromosome Aberration Test with Chinese Hamster V79 Cells," (M. D'Acquisto, Bayer HealthCare AG, PH-GDD Toxicology, Wuppertal, Germany, Study No. T9077203, October 17, 2007). Chinese hamster V79 cells (1 x $10^6$ per 75 $cm^2$ flask) were exposed for 4 hours in duplicate to BYF 14182 (penflufen technical) (95.6%) at 0 (DMSO), 10, 20, 40, 70, and 100 µg/ml without activation and at 0 (DMSO), 15, 30, 60, 75, and 90 µg/ml with rat liver S9 mix. Additionally, duplicate cultures of V79 cells were exposed to BYF 14182 for 18 hours at 0 (DMSO), 3, 6, 12, 24, and 36 µg/ml without activation. Significant reductions in the mitotic indices were noted at 10 µg/ml and above after the 4 hour treatment and at 3 µg/ml and above after the 18 hour treatment without activation vs controls. After 4 hour treatment with rat liver S9 mix, mitotic indices were significantly reduced at 60 and 75 µg/ml vs controls. In the absence of activation, survival indices were 73.4%, 68.5%, and 47.6% of the solvent control value at 40, 70, and 100 µg/ml respectively after the 4 hour treatment and 73.5%, 65.5%, 58.4%, 44.5%, and 45.1% of the solvent control value at 3, 6, 12, 24, and 36 respectively after the 18 hour treatment. With rat liver S9 mix, the survival indices were 91.4%

and 73.6% of solvent controls at 75 and 90 µg/ml respectively after the 4 hour treatment. Cultures treated for 4 hours at 20, 40, and 70 µg/ml in the absence of activation and at 30, 60, and 90 µg/ml with S9 mix were selected for metaphase evaluation. Cultures treated at 3, 6, and 12 µg/ml for 18 hours without activation were subjected to metaphase evaluation. One hundred metaphases per duplicate culture (200 per concentration) were evaluated. No increase in metaphases with aberrations was indicated with or without S9 mix. Positive controls were functional. No increase in structural chromosome aberrations. Acceptable. (Green and Leung, 3/18/13).

**53185-0040 267315, "*In Vitro* Chromosome Aberration Test in Chinese Hamster V79 Cells with BYF 14182," ( C. Hall, Harlan, Cytotest Cell Research GmbH (Harlan CCR), Rossdorf, Germany, Study No. 1271803, August 20, 2009). Chinese hamster V79 cells (6 x $10^4$ cells in each of 2 chambers of a Quadriperm dish) were exposed for 4 hours in duplicate to BYF 14182 (penflufen technical) (94.4%) at 0 (tetrahydrofurane, (THF)), 4.7, 9.4, 18.8, 37.5, 75, 150, 300, 600, and 1200 µg/ml without activation and at 0 (THF), 2.3, 4.7, 9.4, 18.8, 37.5, 50, 75, 100, 150, 300, 600, and 1200 µg/ml with rat liver S9 mix. Additionally, duplicate cultures of V79 cells were exposed to BYF 14182 for 18 hours at 0 (THF), 2.3, 4.7, 9.4, 18.8, 37.5, 50, 75, 100, 150, and 300 µg/ml without activation. In the first trial, precipitation of the test article in culture medium was noted at 300, 600 and 1200 µg/ml with and without rat liver S9 mix. In the second trial, precipitation was not present up to the highest concentration tested, 300 µg/ml, with or without activation. The mitotic index was determined for 1000 cells per culture at each test concentration. Two hundred cells (100 cells per duplicate culture) per test concentration were evaluated for structural chromosomal aberrations. Mitotic indices (% of solvent control) were 91.0% and 0.0% at 37.5 µg/ml and 75 µg/ml respectively without activation and 117.7%, 45.7%, and 17.4% at 37.5, 75, and 150 µg/ml respectively with S9 mix vs the solvent control in the first trial. Second trial mitotic indices were 60.3%, 57.8%, and 0.0% at 9.4, 18.8, and 37.5 µg/ml respectively without activation and 82.5% and 21.6% at 150 µg/ml and 300 µg/ml respectively with S9 mix vs solvent control values. An increase in structural chromosome aberrations was not indicated. Positive controls were functional. No adverse effect. Acceptable. (Green and Leung, 3/20/13).

### DNA damage or miscellaneous effects

**53185-0040 267318, "BYF 14182, Micronucleus Test on the Male Mouse," (B. Herbold, Bayer HealthCare AG, BSP-GDD-GED-GTOX Genetic Toxicology, Wuppertal, Germany, Study No.T 2077981, December 5, 2007). Five male Crl: NMRI BR mice per group received two intraperitoneal injections of BYF 14182 24 (95.6%) twenty-four hours apart at 0 (0.5% Aqueous Cremophor), 250, 500, and 1000 mg/kg followed by bone marrow sampling 24 hours after the second dose. All animals survived to sacrifice. Cytotoxicity (increases in the ratio of normochromatic erythrocytes (NCEs) to 2000 PCEs) was demonstrated at all treated levels with no increase in micronucleated NCEs. An increase in micronucleated polychromatic erythrocytes was not indicated. Positive controls were functional. No increase in cytogenetic damage. Acceptable. (Green and Leung, 3/26/13).

## REPRODUCTIVE TOXICITY, RAT

**53185-0036, 0047 267302, 267363, "Technical Grade BYF 14182: A Two-Generation Reproductive Toxicity Study in the Wistar Rat," ( A.D. Milius, Xenometrics, LLC., Stilwell, KS, Study No. 07-R72-MK, 5 October 2009). Thirty F0 and F1 Wistar Han Crl:WI (HAN) rats per sex per group received BYF14182 (penflufen technical) (95.6%) in the diet at 0 (basal diet), 200, 1000, and 4000 ppm through 2 generations with 1 litter per generation. Group mean BYF 14182 intake during the premating phase was 12.8, 64.1, and 252.2 mg/kg/day for F0 males and 15.0, 75.9, and 294.5 mg/kg/day for F0 females and 12.2, 58.4, and 256.5 mg/kg/day for F1

males and 14.9, 71.2, and 293.4 mg/kg/day for F1 females at 200, 1000, and 4000 ppm respectively. All F0 and F1 parental animals survived to scheduled necropsy without treatment-related clinical signs. Group mean bodyweights were significantly reduced at 4000 ppm for F0 males at treatment weeks 7, 10, 11, and 13 and for F0 females at premating weeks 3 through 10 vs controls. Significant reductions in group mean bodyweight were noted at 4000 ppm for F1 males from the start of treatment (day 0) through week 14 and for F1 females from the start of treatment through premating week 10 vs controls. Group mean bodyweights for F0 and F1 females at 4000 ppm were significantly reduced for gestation days 0, 6, 13, and 20 and for lactation days 0, 4, 7, 14, and 21 vs controls. Significant group mean organ weight changes for F0 and F1 males and females at 4000 ppm included increased liver weights (absolute and relative (% of control)) and decreased thymus weights (absolute (all animals) and relative (F0 females and F1 males and females)) vs controls. Also, absolute spleen weights were significantly decreased for high dose F0 and F1 females vs controls. A significant increase in centrilobular and/or midzonal liver hypertrophy (minimal severity) was noted for F0 and F1 males and females at 4000 ppm vs controls (ns for F1 females). A slight decrease in mean live (day 0) litter size (ns) was noted for F1a and F2a litters at 4000 ppm vs controls. Additionally, the group mean birth index (total number of pups born per litter/total number of implantation sites per dam x 100) was reduced (ns) for both generations at the high dose level vs controls. At 4000 ppm, F1a and F2a group mean pup weights were significantly reduced for lactation days 7, 14, and 21 vs controls. Along with reduced pup weight at the high dose level, preputial separation and vaginal opening was delayed in both generations vs controls (ss for F1a females only). Significant organ weight changes were noted for brain (decreased absolute and increased relative values) and spleen (decreased absolute and relative values) of male and female F1a and F2a pups at 4000 ppm vs controls. No treatment-related effects were noted for estrous cycle activity, sperm parameters, ovarian follicle counts, mating, fertility, gestation indices, days to insemination, or gestation length for F0 or F1 animals. No treatment-related effects were indicated for F2a pup anogenital distance or F1a and F2a gross pathology or histology at any treatment level. Record 267363 is a rat dietary dose- ranging reproductive toxicity study. Parental NOAEL = 1000 ppm (64.1 mg/kg/day for males and 75.9 mg/kg/day for females) based on reduced bodyweight, increased liver weight, and liver histology. Offspring NOAEL = 1000 ppm based on reduced pup weight, changes in brain and spleen weight. Reproductive NOAEL for males > 4000 ppm (256.5 mg/kg/day). Reproductive NOAEL for females = 1000 ppm based on slight reduction in litter size. No adverse effect. Acceptable. (Green and Leung, 2/27/13).

53185-0047 267363, “Technical Grade BYF 14182: A Dose Range-Finding Reproductive Toxicity Study in the Wistar Rat,” (A.D. Milius, Bayer CropScience LP, Residue and Environmental Chemistry Group, Stilwell, KS., Study No. 07-P72-JW, 3 September 2009). Ten F0 Wistar Han CRL: WI (HAN) rats per sex per group received BYF 14182 (penflufen technical) (95.6%) in the diet at 0 (basal diet), 100, 2000, 4000, and 7000 ppm through weaning of 1 F1 litter (day 21 post partum). Group mean achieved dosages during the 10-week premating period were 7.1, 135.4, 290.6, and 494.2 mg/kg/day for males and 9.0, 163.5, 331.4, and 668.7 mg/kg/day for females at 100, 2000, 4000, and 7000 ppm respectively. All F0 males and females survived to scheduled termination, and no treatment-related clinical signs were noted at any treatment level. At 7000 ppm, reductions were noted for F0 group mean bodyweight in males (-10.4% by week 18, (ns)) and females (-7.1% at week 10 (statistically significant) (ss)) and for group mean bodyweight gain in males (-20.4% for weeks 1-13 (ns)) and females (-30.5% for weeks 1-10 (ns)) vs controls. Significant bodyweight reductions were also noted for F0 females at 4000 ppm at week 10 (-8%) vs controls. F0 group mean food consumption was increased for high dose females for premating weeks 1-10 (10.4% (ns)), gestation days 0-20 (73% (ss)), and lactation days 0-21 (23.3% (ns)) vs controls. At necropsy, 2 high dose F0

males had bilaterally reduce testes and epididymides, and the females cohoused with these two males did not become pregnant. F0 group mean relative liver weight (% bodyweight) was significantly increased for males at 2000, 4000, and 7000 ppm and for females at 7000 ppm vs controls. Group mean day 21 pup weights were reduced at 4000 ppm (-8.1% (ns)) and 7000 ppm (-15.4% ($p \leq 0.01$)) vs controls. Parental NOEL males = 100 ppm (7.1 mg/kg/day) based on liver weight and females = 2000 ppm (163.5 mg/kg/day for) based on bodyweight. Reproductive NOEL for males = 4000 ppm (290.6 mg/kg/day) based on reduced testes and epididymides and for females > 7000 ppm (668.7 mg/kg/day). Pup NOEL = 4000 ppm (290.6 mg/kg/day for males and 331.4 mg/kg/day for females) based on pup weights. Supplemental data. (Green, 2/8/13). No worksheet.

## DEVELOPMENTAL TOXICITY

### Rat

**53185-0035 267300, "BYF 14182, Developmental Toxicity Study in the Rat by Gavage", ( C. Langrand-Lerche, Bayer CropScience, Sophia Antipolis, France, Study No. SA 06329, September 12, 2008). Twenty-three sperm-positive female Crl:CD (SD) Sprague-Dawley (IGS BR) rats per group received BYF 14182 (penflufen technical) (95.6%) by oral gavage at 0 (0.5% aqueous methylcellulose 400), 30, 100, and 300 mg/kg/day on gestation days 6 to 20. All dams survived to scheduled necropsy with no treatment-related clinical signs. Group mean maternal bodyweight gain at 300 mg/kg/day was significantly reduced for gestation days 6 to 21 (and intervals 6 to 8, 10, 14, and 18) vs controls. At the mid dose, group mean maternal bodyweight was reduced 32% (gestation days 6 to 8) and 18% (gestation days 8 to 10) compared to controls (ns). Group mean maternal food consumption was significantly reduced at the high dose for gestation days 8 to 10 compared to controls. Group mean maternal absolute liver weights were significantly increased at 300 mg/kg/day vs controls. Necropsy revealed prominent lobulation of the liver in 3/23 dams at 100 mg/kg/day and 4/23 females at 300 mg/kg/day, respectively. There were no treatment-related effects on pregnancy rate, pre- and post implantation loss, early or late resorptions, fetal death status, percentage of male and female fetuses, fetal bodyweights, fetal external observations, fetal visceral examinations, or fetal skeletal evaluations at any treatment level. Maternal NOEL = 30 mg/kg/day based on liver changes. Developmental NOEL = 300 mg/kg/day. Teratogenicity was not indicated. Acceptable. (Green and Leung, 1/9/13).

53185-0046 267362, "Range-Finding Study with Fetal Evaluation for Developmental Toxicity in the Rat by Gavage", ( A. Mc Elligott, Bayer CropScience, Sophia Antipolis, France, Study No. SA 04192, June 30, 2005). Eight sperm positive female Sprague Dawley rats per group received BYF 14182 (penflufen technical) (98.6%) by oral gavage at 0 (0.5% aqueous methylcellulose 400), 50, 300, and 1000 mg/kg/day on gestation days 6 to 20. One high dose female showing marked clinical signs (soiled mouth and anogenital region, reduced motor activity) and bodyweight loss was sacrificed on gestation day 19 (necropsy revealed mottled kidneys, prominent lobulation of the of liver, multiple black foci in stomach, enlarged adrenal glands, and dark content in the intestine). Group mean bodyweight gain was significantly reduced (27%) for high dose animals during gestation days 6 to 21 vs controls. Also, at the high dose level, group mean food consumption was significantly reduced for gestation days 6 to 8 and 18 to 21 vs controls. At scheduled necropsy, group mean maternal liver weights were increased (29%) at the high dose level compared to controls. At Cesarean section, group mean fetal weight (both sexes) at 1000 mg/kg/day was significantly reduced (6.4%) compared to controls. One mid dose dam was sacrificed at gestation day 18 following a gavage error. Group mean maternal bodyweight change for gestation days 6 to 21 was marginally reduced (4%, ns) at the mid dose vs controls. Group mean fetal weight was significantly reduced (5.1%)

at the mid dose vs controls. At 50 mg/kg/day, group mean bodyweight gain for gestation days 6 to 21 was comparable to controls. At Cesarean sectioning, low dose group mean fetal weight was significantly reduced (2.9%) compared to controls (values were within the range of historical control data). No treatment-related findings were noted for fetal external, visceral, and skeletal evaluations at any treatment level. Supplemental data. (Green, 1/8/13). No worksheet.

### Rabbit

**53185-0035, 0047 267301, 267364, "BYF 14182, Developmental Toxicity Study in the Rabbit by Gavage", (P. Kennel, Bayer CropScience, Sophia Antipolis, France, Study No. SA 06330, September 23, 2008). Twenty-three time-mated female New Zealand White Crl:KBL (NZW) rabbits per group received BYF 14182 (penflufen technical) (95.6%) by oral gavage at 0 (0.5% aqueous methylcellulose 400), 30, 100, and 600 mg/kg/day on gestation days 6 to 28. One 600 mg/kg/day dam was sacrificed for humane reasons (few or no feces and bodyweight loss) on gestation day 25. Additionally, 2 mid dose dams and 1 control dam were found dead, and 1 low dose dam was sacrificed due to dosing errors. Group mean maternal bodyweight change was significantly reduced at 600 mg/kg/day for gestation days 6 to 14, 6 to 22, and 6 to 26 relative to controls (values at the low and mid dose levels were comparable to controls for all time intervals). Additionally, group mean maternal food consumption was decreased for all intervals at the high dose level for gestation days 6 to 22 vs controls (with statistical significance for days 6 to 8, 8 to 10, 14 to 18, and 18 to 22). No treatment-related effects were indicated for pre- and post -implantation loss, early or late resorptions, number of *corpora lutea*, fetal death status, or percentage of male and female fetuses at any dose level. Group mean fetal weights (for individual sexes and combined) were 7% to 8% lower than control values at 600 mg/kg/day (no statistical significance). No treatment-related effects were noted for fetal external, visceral, or skeletal evaluations at any dose level. Record 267364 is a range-finding oral (gavage) developmental toxicity study in rabbits. Maternal NOEL = 100 mg/kg/day based on reduced bodyweight and food consumption. Developmental NOEL = 100 mg/kg/day based on reduced fetal weights. Teratogenicity was not indicated. Acceptable. (Green and Leung, 1/11/13).

53185-0047 267364, "BYF 14182, Range-Finding Study for Developmental Toxicity in the Rabbit by Gavage", (P. Kennel, Bayer CropScience, Sophia Antipolis, France, Study No. SA 04193, March 14, 2005). Eight time-mated female New Zealand White rabbits per group received BYF 14182 (penflufen technical) (98.6%) by oral gavage at 0 (0.5% aqueous methycellulose 400), 100, 300, 600, and 1000 mg/kg/day on gestation days 6 to 28. Two high dose females were sacrificed, 1 on gestation day 20 for humane reasons (reduced bodyweight and food consumption, few or no feces), and, the other on day 24 after it aborted. Clinical signs in surviving high dose animals included increased incidences of few or no feces (4/6 animals), soft feces (3/6 females), and localized hair loss on the last study day (2/6 animals) compared to controls. At cesarean sectioning, pre-implantation loss per dam was increased and the number of live fetuses per litter was decreased at 1000 mg/kg/day compared to controls. At 600 mg/kg/day, there were no maternal deaths or abortions and treatment-related clinical signs included few feces on 1 or more occasions in 4/8 dams; soft feces on a few occasions in 1/8 females; and localized hair loss (1 or more times) in 4/8 dams. Also at 600 mg/kg/day, group mean maternal bodyweight decrease (gestation days 6 to 18) and/or reduced group mean maternal bodyweight gain (gestation days 6 to 18 and 6 to 29) was noted vs controls. Group mean maternal food consumption at 600 mg/kg/day was reduced up to 29% for gestation days 6 to 18 compared to controls. Group mean fetal bodyweight was reduced (7%) and the group mean percentage of runt fetuses and of litters with runt fetuses was increased at 600 mg/kg/day compared to controls. At 300 mg/kg/day, two females were sacrificed, 1 on gestation day 19 after aborting, and the other, on gestation day 25 for humane reasons (marked reduction in

bodyweight and food consumption). No treatment-related litter or fetal parameter changes were indicated at 300 mg/kg/day. At 100 mg/kg/day, no treatment-related effects were noted for maternal deaths, abortions, clinical signs, bodyweight change, food consumption, or litter and fetal parameters. Supplemental data. (Green, 1/10/13). No worksheet.

## NEUROTOXICITY

### Rat Acute Neurotoxicity Study

**53185-0041 267319, "An Acute Oral Neurotoxicity Screening Study with Technical Grade BYF 14182 in Wistar Rats," ( R.G. Gilmore, Bayer CropScience LP, Toxicology, Stilwell, KS., Report No. 201967, January 28, 2009). Twelve Wistar Han Crl:WI (HAN) rats per sex per group received a single oral gavage dose of BYF 14182 (penflufen technical) (95.6%) at 0 (0.5% (w/v) methylcellulose/0.4% (w/v) Tween 80 in deionized water), 100, 500, and 2000 mg/kg followed by a 14 day observation period. Since compound-related effects were noted for motor and locomotor activity at 100 mg/kg in females, a follow-up study with 12 females per group receiving a single oral gavage dose of BYF 14182 at 0 (vehicle), 25, and 50 mg/kg was conducted to establish an overall No-Observed-Adverse-Effect Level (NOAEL) in females. All animals survived to terminal sacrifice. Treatment-related clinical signs in the initial study included increases in urine stain in males and females at 500 mg/kg and 2000 mg/kg, in stiff-legged hind-limbs, ataxia, and decreased activity, and in clear lacrimation for mid and high dose females vs controls. Clinical signs in mid and high dose males and females were first seen on the day of dosing and resolved 1 to 3 days post treatment. No treatment-related clinical signs were indicated for follow-up study females at 25 and 50 mg/kg vs controls. Treatment-related functional observational battery (FOB) results for the initial study included significant decreases in group mean body temperature on the day of dosing for mid (37.7°C) and high dose females (37.7°C) vs controls (38.5°C), and two high dose males were noted with slight to moderate yellow stain on the day of dosing vs the control incidence, 0/12. No treatment-related FOB results were noted for the follow-up study females. Motor activity and locomotor activity for the overall 60-minute test session in the initial study were significantly reduced on the day of dosing (Day 0) for mid and high dose males and females and for low dose females vs controls. Values for low dose males and follow-up study females were comparable to control results. At terminal necropsy of initial study animals, no treatment-related effects were noted for gross lesions or terminal bodyweight (all animals), or brain weight (perfusion-fixed animals) at any dose level vs controls. No treatment-related histology changes were noted for neural tissues from high dose perfusion-fixed males or females. Systemic NOEL = 100 mg/kg for males and 50 mg/kg for females based on clinical signs and motor and locomotor activity. Adverse effects were not indicated. Acceptable. (Green, 2/21/13).

### Rat 13-Week Dietary Neurotoxicity Study

**53185-0042 267320, "A Subchronic Neurotoxicity Screening Study with Technical Grade BYF 14182 in Wistar Rats", ( R.G. Gilmore, Bayer CropScience LP, Toxicology, Stilwell, KS., Report No. 201961, January 27, 2009). Twelve Wistar Han Crl:WI (HAN) rats per sex per group received BYF 14182 (penflufen technical) (95.6%) in the diet at 0 (basal diet), 250, 2000, and 8000 ppm for 13 weeks. Group mean daily intake of BYF 14182 was 16.02, 126.1, and 516.0 mg/kg/day for males and 19.88, 155.9, and 608.8 mg/kg/day for females at 250, 2000, and 8000 ppm during the 13 week treatment period respectively. No treatment-related effects were noted for clinical signs, mortality, FOB, motor and locomotor activity, gross pathology, or neuropathology. Group mean bodyweights were significantly reduced at treatment weeks 4,5,6, and 7 for males and at treatment weeks 1 through 13 inclusive for females at 8000 ppm vs controls. Group mean food consumption at the high dose level was significantly decreased for treatment weeks 3 (-10%) and 5 (-9%) for males and for treatment weeks 2 through 13 inclusive

for females vs controls. Additionally, group mean food consumption was decreased (-7% to -12%) for mid dose females from treatment weeks 2 through 13 inclusive (statistically decreased for weeks 2, 4, 5, 6, 7, 9, 10, 11, and 13) vs controls. Group mean relative liver weights (% bodyweight) for non-perfused animals were significantly increased for mid and high dose males (13% and 23% respectively) and females (12% and 28% respectively) vs controls. Systemic NOEL = 250 ppm (16.02 mg/kg/day in males and 19.88 mg/kg/day in females) based on liver weights. Neurotoxicity NOAEL = 8000 ppm (516.0 mg/kg/day in males and 608.8 mg/kg/day in females). No adverse effect. . (Green, 2/13/13).

### Developmental neurotoxicity, rat

Study not submitted nor required at this time.

### Delayed neurotoxicity, hen

Study not submitted nor required at this time.

## IMMUNOTOXICITY

### Rat 4-Week Dietary Immunotoxicity Study

**53185-0045 267358, "Subacute Oral Immunotoxicity Study in Wistar Rats (4 Weeks Administration by Diet)," (L. Schladt and H.W. Vohr, Bayer HealthCare AG, Wuppertal, Germany, Study No. T6078515, September 3, 2008). Eight Wistar (Hsd Cpb:WU) rats per sex per group received BYF 14182 (penflufen technical) (95.6%) in the diet at 0 (basal diet), 200, 1000, and 7000 ppm for 4 weeks. Group mean achieved dosage levels were 17.9, 82.6, and 755.6 mg/kg/day for males and 20.4, 104.5, and 960.5 mg/kg/day for females at 200, 1000, and 7000 ppm, respectively. All animals survived to scheduled necropsy, and no treatment-related clinical signs were indicated. Group mean terminal bodyweights were significantly reduced for males and females at 7000 ppm compared with controls (bodyweight was also slightly reduced for mid dose females (ns) vs controls). Group mean food consumption was increased for both sexes (ns) at 7000 ppm vs controls. Group mean spleen weights, thymus weights, and total spleen cell counts at all treatment levels were comparable to controls. Suppression of plaque forming cells was not indicated at any treatment level. Immunotoxicity was not indicated. Systemic NOAEL = 1000 ppm (82.5 mg/kg/day for males and 104.5 mg/kg/day for females) based on reduced bodyweights. Immunotoxicity NOEL = 7000 ppm (755.6 mg/kg/day for males and 960.5 mg/kg/day for females). Acceptable. (Green, 1/17/13).

## ENDOCRINE DISRUPTOR STUDIES

Study not submitted nor required at this time.

## SUPPLEMENTAL STUDIES

## MUTAGENICITY STUDIES WITH METABOLITES OF PENFLUFEN

## GENE MUTATION

**53185-0040 267308, "BYF 14182-3-Hydroxy-Butyl, Salmonella/Microsome Test, Plate Incorporation and Preincubation Method," (B. Herbold, Bayer HealthCare AG, BSP-GDD-GED-GTOX Genetic Toxicology, Wuppertal, Germany, Study No. T 1078727, April 7, 2008). Triplicate cultures of *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were exposed to BYF 14182-3-hydroxy-butyl (98.5%) (a metabolite of BYF 14182), in the presence and absence of rat liver S9 mix, at 0 (DMSO), 16, 50, 158, 500, 1581, and 5000 $\mu$g/plate for 48 hours (at 37°C) after plate incorporation. In a second trial at the same treatment levels, cultures were preincubated for 20 minutes prior to plating. Precipitation was noted at

5000 μg/plate in the presence and absence of activation. Background lawn growth and bacterial titer was comparable to solvent controls. There were no increases in the number of revertants per plate compared to the solvent controls. Positive controls were functional. No adverse effect. Acceptable. (Green and Leung, 3/5/13).

**53185-0040 267309, "BYF 14182-pyrazolyl-AAP, Salmonella/Microsome Test, Plate Incorporation and Preincubation Method," (B.Herbold, Bayer Schering Pharma AG, GDD-GED-GTOX Genetic Toxicology, Wuppertal, Germany, Study T 1080085, June 8, 2009). Triplicate cultures of *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were exposed to BYF 14182-pyrazolyl-AAP (99.6%), in the presence and absence of rat liver S9 mix, at 0 (DMSO), 16, 50, 158, 500, 1581, and 5000 μg/plate for 48 hours (at 37°C) after plate incorporation. In a second trial at the same treatment levels, cultures were preincubated for 20 minutes prior to plating. Precipitation was noted at 500, 1581, and 5000 μg/plate in the presence and absence of activation in both trials. Background lawn growth and bacterial titer at all treatment levels was comparable to solvent controls in both trials. There were no increases in the number of revertants per plate at any treatment level compared to the solvent controls. Positive controls were functional. No adverse effect. Acceptable. (Green and Leung, 3/6/13).

**53185-0040 267312, "BYF 14182-3-hydroxy-butyl, V79/HPRT-Test *In Vitro* for the Detection of Induced Forward Mutations," (G. Entian, Bayer HealthCare AG, BSP-GDD-GED-GTOX Genetic Toxicology, Wuppertal, Germany, Study No. T 4078702, April 21, 2008). Exponentially growing V79 cells (4 x $10^6$) were plated (75 $cm^2$ flasks) in duplicate and treated with BYF 14182-3-hydroxy-butyl (98.5%) (a metabolite of BYF 14182) for 5 hours at untreated, 0 (DMSO), 75, 150, 300, 600, 900, and 1200 μg/ml in the presence and absence of rat liver S9 mix. Two trials were performed. Precipitation was noted at 900 and 1200 μg/ml without S9 mix and at 600, 900, and 1200 μg/ml with S9 mix. Positive controls were functional. Cloning efficiency at all treated levels was comparable to solvent control values with and without S9 mix. An increase in forward gene mutations was not indicated in the presence or absence of rat liver S9 mix. Acceptable. (Green and Leung, 3/12/13).

**53185-0040 267313, "BYF 14182-Pyrazolyl-AAP, V79/HPRT-Test *In Vitro* for the Detection of Induced Forward Mutations," (G. Entian, Bayer Schering Pharma AG, GDD-GED-GTOX Genetic Toxicology, Wuppertal, Germany, Study No. T 3080087, August 26, 2009). Exponentially growing V79 cells (4 x $10^6$) were plated (75 $cm^2$ flasks) in duplicate and treated with BYF 14182-pyrazolyl-AAP (99.6%) for 5 hours at untreated, 0 (DMSO), 3, 6, 12, 24, 36, 48, and 60 μg/ml in the presence and absence of rat liver S9 mix. Two trials were performed. Precipitation was noted at 60 μg/ml in the absence of S9 mix. Cloning efficiency at all treated levels was comparable to solvent control values with or without S9 mix. An increase in forward gene mutations was not indicated in the presence or absence of S9 mix. Acceptable. (Green and Leung, 3/13/13).

## CHROMOSOME EFFECTS

**53185-0040 267316, "BYF 14182-3-Hydroxy-Butyl, *In Vitro* Chromosome Aberration Test with Chinese Hamster V79 Cells," (M. Nern, Bayer HealthCare AG, BSP-GDD-GED-GTOX Genetic Toxicology, Wuppertal, Germany, Study No. T 3078701, April 4, 2008). Chinese hamster V79 cells (1 x $10^6$ per 75 $cm^2$ flask) were exposed for 4 hours in duplicate to BYF 14182-3-hydroxy-butyl (98.5%) (a metabolite of BYF 14182) at 0 (DMSO), 150, 300, 600, 900, and 1200 μg/ml without activation and at 0 (DMSO), 75, 150, 300, 600, and 900 μg/ml with rat liver S9 mix. Additionally, duplicate cultures of V79 cells were exposed to BYF 14182-3-hydroxy-butyl for 18 hours at 0 (DMSO), 75, 150, 300, 450, and 600 μg/ml without activation.

Test article precipitation was noted in the medium at 900 µg/ml (+/- S9 mix) and 1200 µg/ml (- activation) during the 4 hour treatment period and at the high dose, 600 µg/ml, during the 18 hour exposure (- activation). The mitotic index was determined for 1000 cells per culture at each test concentration. Two hundred cells (100 cells per duplicate culture) per test concentration were evaluated for structural chromosomal aberrations. Mitotic indices were significantly reduced at 600, 900, and 1200 µg/ml after the 4 hour treatment and at 450 and 600 µg/ml after the 18 hour treatment without activation vs solvent controls. Significant reductions in the mitotic index were also noted at 300 and 600 µg/ml with rat liver S9 mix after the 4 hour exposure period vs the solvent controls. No increase in metaphases with aberrations was indicated after the 4 hour treatment with and without rat liver S9 mix or after the 18 hour treatment without activation vs solvent controls. Positive controls were functional. No increase in structural chromosome aberrations. Acceptable. (Green and Leung, 3/22/13).

**53185-0040 267317, "BYF 14182-Pyrazolyl-AAP, *In Vitro* Chromosome Aberration Test with Chinese Hamster V79 Cells," (M. Thum, Bayer HealthCare AG, GDD-GED-GTOX Genetic Toxicology, Wuppertal, Germany, Study No. T 2080086, August 24, 2009). Chinese hamster V79 cells (1 x $10^6$ per 75 $cm^2$ flask) were exposed in duplicate to BYF 14182-pyrazolyl-AAP (99.6%) at 0 (DMSO), 15, 30, and 60 µg/ml with and without rat liver S9 activation for 4 hours and without activation for 18 hours. Test article precipitation in the medium was noted at 30 and 60 µg/ml (-S9 mix) and at 60 µg/ml (+ S9 mix) after the 4 hour treatment and at 60 µg/ml after the 18 hour treatment (- S9 mix). Mitotic indices were 103.0%, 107.8%, and 99.6% without activation and 120.4%, 88.1%, and 118.1% with S9 mix after the 4 hour treatment and 100.0%, 85.0%, and 80.0% without activation after the 18 hour treatment at 15, 30, and 60 µg/ml respectively vs the solvent controls. No increase in metaphases with aberrations was indicated after the 4 hour treatment with and without rat liver S9 mix or after the 18 hour treatment without activation vs solvent controls. Positive controls were functional. No increase in the frequency of structural chromosome aberrations. Acceptable. (Green and Leung, 3/25/13).

## MECHANISTIC STUDIES

53185-0054; 287880; "7-Day Live Mechanistic Study in the Female Rat by Dietary Administration (Histopathology, Cell Proliferation, Enzyme Activity, and Gene Transcript Investigations)"; (O. Blanck; Bayer S.A.S, Bayer CropScience, 06903 Sophia Antipolis Cedex, France; Study No. SA 12148; 1/14/13); Five Wistar female rats/group received 0 or 7000 ppm of penflufen technical (batch no. PFV114A008, purity: 99.6%) in the diet for 7 days (595 mg/kg/day). As a positive control, 5 female rats were dosed daily orally by gavage with 80 mg/kg/day of phenobarbital for 7 days. Each animal received 80 mg/100 ml of 5-bromo-2'-deoxyuridine (BrdU) in the drinking water. On day 8, the animals were euthanized. Brain and liver weights were recorded. Sections of liver were examined histologically. Additional sections of liver were assayed for BrdU staining and cell proliferation was assessed. Activities of selected hepatic enzymes were assayed. Total cytoplasmic RNA was purified from liver samples and the quantitative polymerase chain reaction (Q-PCR) assay was employed to identify and measure gene transcripts. The mean relative liver weight of the penflufen-treated group was greater than that of the control ($p<0.01$). The mean absolute and relative liver weights of the phenobarbital-treated group were greater than the control group values ($p<0.05$ or 0.01). In the histopathological evaluation, hepatocellular hypertrophy was noted in two of the five phenobarbital-treated animals. The cell proliferation assay revealed increased BrdU labeling in both the centrilobular and periportal regions of the penflufen-treated animals. For the phenobarbital-treated animals, labeling was increased only in the centrilobular region. The cytochrome P-450 enzyme content was elevated in both the treatment groups ($p<0.05$ or 0.01). Among the hepatic enzymes which were assayed, phase I enzymes, PROD and BROD

activities were increased in comparison to the control levels (NS, p<0.05 or 0.01). Lauric acid hydrolase was not elevated. Phase II enzymes, UDPGT-4-nitrophenol and UDPGT-bilirubin activities were elevated as well for both of the treatment groups (p<0.01). The increases noted for the gene transcripts correlated with these increased phase I enzyme activity levels (PROD: increased level of Cyp2b1), (BROD: increased level of Cyp3a3). The lauric acid hydrolase gene transcript, Cyp4a1, was not increased for either treatment group. For the phase II enzyme, UDP-glucuronyl transferase, both gene transcripts, Ugt1a6 and Udpgtr2, were increased for both treatment groups. The only anomaly was the lack of significantly increased activity for EROD in the livers of the penflufen-treated animals despite the increase in the correlated gene script, Cyp1a1. For the other transcripts which were assayed, the gene transcript for epoxyhydrolase, Ephx1 was increased for both groups. The glutathione- S-transferase gene transcript, Gstm4, was increased only for the phenobarbital-treated animals. In contrast, the gene transcript for P-450 oxydoreductase, Por, was reduced for both treatment groups. **Study supplemental.** (Moore, 12/24/15)

53185-0055; 287881; "7-Day Live Mechanistic Study in the Male Mouse by Dietary Administration (Histopathology, Cell Proliferation, Enzyme Activity, and Gene Transcript Investigations)"; (O. Blanck; Bayer S.A.S, Bayer CropScience, 06903 Sophia Antipolis Cedex, France; Study No. SA 13036; 9/19/13); Twenty five C57BL/6J male mice/group received 0 or 6000 ppm of penflufen technical (batch no. PFV114A008, purity: 99.6%) in the diet for 7 days (1041 mg/kg/day). As a positive control, 25 male mice were dosed orally by gavage with 80 mg/kg/day of phenobarbital for 7 days. Each animal received 80 mg/100 ml of 5-bromo-2'-deoxyuridine (BrdU) in the drinking water. On day 8, the animals were euthanized. Brain and liver weights were recorded. Sections of liver were examined histologically. Additional sections of liver were assayed for BrdU staining and cell proliferation was assessed. Activities of selected hepatic enzymes were assayed. Total cytoplasmic RNA was purified from liver samples and the quantitative polymerase chain reaction (Q-PCR) assay was employed to identify and measure gene transcripts. The mean absolute and relative liver weights of the penflufen-treated group was greater than that of the control (p<0.001). The mean absolute and relative liver weights of the phenobarbital-treated group were not affected by the treatment. In the histopathological evaluation, hepatocellular hypertrophy was noted in twenty four of the 25 mice treated with penflufen and in all of the mice in the phenobarbital group. The cell proliferation assay revealed increased BrdU labeling in the centrilobular and periportal regions of both the penflufen- and phenobarbital-treated animals with a greater degree of proliferation noted for the phenobarbital group. The cytochrome P-450 enzyme content was elevated in both the treatment groups (p<0.001). The phase I enzymes, EROD, PROD and BROD activities were increased in comparison to the control levels for both treatment groups (p<0.001). Lauric acid hydrolase activity was not induced by either treatment. Phase II enzyme, UDPGT-bilirubin activities was elevated as well for both of the treatment groups (p<0.001). The increases noted for the gene transcripts correlated with these increased phase I enzyme activity levels in both treatment groups (PROD: increased levels of Cyp2b9 and/or Cyp2b10, BROD: increased level of Cyp3a11). Similarly the gene transcript for lauric acid hydrolase, Cyp4a10, was slightly elevated for the penflufen group and corresponded with the slight increase in enzyme activity. For the phase I enzyme, EROD, the gene transcript, Cyp1a1, did not correlate as well with the increase in observed activity (penflufen-treated animals: NS, phenobarbital-treated animals: p<0.05). For the phase II enzyme, UDP-glucuronyl transferase, the gene transcripts, Ugt1a1, Ugt2b1 and Ugt2b5, were increased for both treatment groups (p<0.01 or 0.001). In addition, the gene transcripts for epoxyhydrolase, Ephx1 and for glutathione-S-transferase, Gstm4, were increased for both treatment groups (p<0.01, or 0.001). The sulfotransferase gene transcripts, Sult1a1, Sult2a2 and Sultn, were increased for the phenobarbital-treated group (p<0.01 or 0.001). For the penflufen- treated animals, only Sultn was increased (p<0.05). The gene

transcript for P-450 oxydo- reductase, Por, was elevated for the phenobarbital group ($p<0.001$) and not for the penflufen group. **Study supplemental.** (Moore, 12/29/15)