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

# SUMMARY OF TOXICOLOGY DATA
# ACTIVE INGREDIENT: CYFLUMETOFEN

Chemical Code # 6083, Document Processing Number (DPN) # 53174
SB 950 # None assigned
Original date: 01/10/2013
Revised date: 01/21/2016

## DATA GAP STATUS

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

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Toxicology one-liners are attached.

All record numbers for the above study types through 274706 (Document No. 53174-0103) were examined. This includes all relevant studies indexed by DPR as of 01/21/2016.

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:
Revised by Corlett, 01/21/2016

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

53174-0053; 264921; "[$^{14}$C] OK-5101 (Phenyl-ring-U and Tolyl-ring-U-Label): Metabolic Fate in Rats (Pharmacokinetics)"; (H. Nakamura; The Institute of Environmental Toxicology, Mitsukaido-shi, Ibaraki 303-00432, Japan; Study ID No. IET 02-8003-1; 6/17/04); Four Fischer 344 rat/sex/group were dosed with 3 or 250 mg/kg of [A-$^{14}$C]OK-5101 (lot no. CFQ12735, specific activity: 1.37 GBq/mmol, radiochemical purity: 99.2%) or 3 or 250 mg/kg of [B-$^{14}$C]OK-5101 (lot no. CFQ12736, specific activity: 1.37 GBq/mmol, radiochemical purity: 98.1%). Unlabeled OK-5101 technical (lot no. 01E1, purity: 98.46%) was used to adjust the specific activity of the dosing preparations. Blood samples were drawn periodically between 0.25 to 72 hours post-dose. Overall, the position of the radiolabel did not significantly affect the various parameters. The only apparent difference between the sexes was the higher Cmax for the females in the 250 mg/kg treatment groups. The time to tmax was 1.0 hour for the 3 mg/kg treatments and ranged from 2.0 to 4.0 hours for the 250 mg/kg treatments. Cmax ranged from 0.95 to 1.34 mg equivalents/L for the 3 mg/kg groups and from 10.01 to 15.37 mg equivalents/L for the 250 mg/kg groups. The t1/2 for the beta-phase of elimination ranged from 13.9 to 21.8 hours for the 3 mg/kg treatments and from 12.4 to 21.8 hours for the 250 mg/kg treatments. **Study supplemental.** (Moore, 7/30/12)

53174-0053; 264922; "[$^{14}$C] OK-5101 (Phenyl-ring-U and Tolyl-ring-U-Label): Metabolic Fate in Rats (Tissue Distribution); (H. Nakamura; The Institute of Environmental Toxicology,

Mitsukaido-shi, Ibaraki 303-00432, Japan; Study I D No. IET 02-8003-3; 7/2/4); Six Fischer 344 rat/sex/group were dosed with 3 or 250 mg/kg of [A-$^{14}$C]OK-5101 (lot no. CFQ12735, specific activity: 1.37 GBq/mmol, radiochemical purity: 99.2%) or 3 or 250 mg/kg of [B-$^{14}$C]OK-5101 (lot no. CFQ12736, specific activity: 1.37 GBq/mmol, radiochemical purity: 98.1%). Unlabeled OK-5101 technical (lot no. 01E1, purity: 98.46%) was used to adjust the specific activity of the dosing preparations. Three animals/sex/group/time point were euthanized at the Tmax (1 hour post-dose for the 3 mg/kg groups and 2 hours post-dose for the 250 mg/kg groups) and 24 hours post-dose. Tissue/organs were assayed for residual radioactivity. A majority of the administered dose was isolated in the gastrointestinal tract up to 24 hours post-dose. Otherwise, the kidneys and liver were the primary organs in which the radiolabeled test material was isolated. Only in these two organs was the tissue to plasma concentration ratio greater than one. The biological half-lives of the radiolabel in the tissues were comparable for the majority of the tissues assessed. However, the half-life value of the adipose tissue was approximately two times greater than that of the plasma at 3 mg/kg and 2.3 to 4 times greater than the plasma value at 250 mg/kg. This longer half life did not result in increased tissue concentration of the radiolabel in the fat. **Study supplemental.** (Moore, 7/31/12)

53174-0054; 264923; "[$^{14}$C] OK-5101 (Phenyl-ring-U and Tolyl-ring-U-Label): Metabolic Fate in Rats (Quantitation and Identification of Metabolites in Urine and Feces)"; (K. Ohyama; The Institute of Environmental Toxicology, Mitsukaido-shi, Ibaraki 303-00432, Japan; Study ID No. IET 02-8003-5; 7/13/04); The radiolabel recovered from the urine and feces in Study ID No. IET 02-8003-2 was analyzed for metabolites. Metabolism of the parent compound entailed cleavage of the bonds around the central carbon resulting in three separate moieties, 1) AB-1 in which the carboxyl ester bond was cleaved and 2) A-1 and B-1 in which the tert-butylphenyl group and the trifluorotolyl group were formed from the cleavage of the ketone linkage. Further modifications included the oxidative reactions to hydroxyl and carbonyl moieties. Secondary conjugation reactions with glutathione and glucuronic acid resulted in the isolation of [B-1] mercapturic acid and [B-1] thiolactic acid conjugates and the [A-6] glucuronic acid conjugate, respectively. For the A-ring labeled compound, A-18 and A-21 were the predominant metabolites for the 3 mg/kg treatment group. B-1, [B-1]MA and [B-1]TLA constituted the highest percentage of metabolites for the B-ring labeled compound. Three to 4% of the administered dose was recovered as the parent compound. In the 250 mg/kg group, the percentage of the parent compound which was recovered rose to 54 to 66% of the administered dose, largely in the feces. The percentages of the other metabolites were concomitantly reduced. AB-3 was the one metabolite which demonstrated a sex-difference. It was more readily recovered in the urine of the females than that of the males (3 mg/kg: (M) 0.05 to 0.07% vs. (F) 8 to 9%, 250 mg/kg: (M) 0.04 to 0.09% vs. (F) 5 to 6%). **Study supplemental.** (Moore, 8/8/12)

53174-0054; 264924; "[$^{14}$C] OK-5101 (Phenyl-ring-U and Tolyl-ring-U-Label): Metabolic Fate in Rats (Biliary Excretion Study)"; (H. Nakamura; The Institute of Environmental Toxicology, Mitsukaido-shi, Ibaraki 303-00432, Japan; Study ID No. IET 02-8003-4; 6/30/04). Three or four bile duct-cannulated Fischer 344 rats/sex/group were dosed with 3 or 250 mg/kg of [A-$^{14}$C]OK-5101 (lot no. CFQ12735, specific activity: 1.37 GBq/mmol, radiochemical purity: 99.2%) or 3 or 250 mg/kg of [B-$^{14}$C]OK-5101 (lot no. CFQ12736, specific activity: 1.37 GBq/mmol, radiochemical purity: 98.1%). Unlabeled OK-5101 technical (lot no. 01E1, purity: 98.46%) was used to adjust the specific activity of the dosing preparations. Bile, urine and feces

were collected at specified intervals up to 48 hours post-dose. The recovery of radiolabel in the bile was higher for the males than for the females (3 mg/kg: (M) 36 to 37% vs. (F) 24 to 25%, 250 mg/kg: (M) 29 to 32% vs. (F) 18 to 21%). Excretion via the urine was inversely related with the males demonstrating a lower recovery of the radiolabel (3 mg/kg: (M) 29 to 30% vs. (F) 41 to 51%, 250 mg/kg: (M) 11 to 15% vs. (F) 16 to 24%). Recovery of the radiolabel in the feces was greatly increased for the 250 mg/kg treatment groups (3 mg/kg: 6 to 17% vs. 250 mg/kg: 34 to 41%). Absorption ranged from 69 to 80% for the 3 mg/kg treatment groups, diminishing to 36 to 46% for the 250 mg/kg treatment groups. **Study supplemental** (study limited to biliary excretion balance characterization). (Moore, 8/9/12)

53174-0055; 264925; "[$^{14}$C] OK-5101 (Phenyl-ring-U and Tolyl-ring-U-Label): Metabolic Fate in Rats (Quantitation and Identification of Metabolites in Bile)"; (K. Ohyama; The Institute of Environmental Toxicology, Mitsukaido-shi, Ibaraki 303-00432, Japan; Study ID No. IET 02-8003-6; 6/24/04); The radiolabel recovered from the bile in Study ID No. IET 02-8003-4 was analyzed for metabolites. Metabolism of the parent compound entailed cleavage of the bonds around the central carbon resulting in three separate moieties, 1) AB-1 in which the carboxyl ester bond was cleaved and 2) A-1 and B-1 in which the tert-butylphenyl group and the trifluorotolyl group were formed from the cleavage of the ketone linkage. For the metabolites recovered in the bile, the predominant moieties were derived from the cleavage of the carbonyl bond. Further modifications included the oxidative reactions to hydroxyl and carbonyl moieties. Secondary conjugation reactions with glucuronic acid resulted in the isolation of [A-6] GA, [AB-3] GA, [A-22] GA and [AB-1] GA in the bile. These moieties constituted 61 to 68% of the total radiolabel recovered from the bile of the 3 mg/kg groups and 47 to 56% of the total in the bile of the 250 mg/kg group. **Study supplemental.** (Moore, 8/10/12)

53174-0055; 264926; "[$^{14}$C] OK-5101 (Phenyl-ring-U and Tolyl-ring-U-Label): Metabolic Fate in Rats (Elimination Balance); (H. Nakamura; The Institute of Environmental Toxicology, Mitsukaido-shi, Ibaraki 303-00432, Japan; Study ID No. IET 02-8003-2; 6/17/04); Four Fischer 344 rats/sex/group were dosed with 3 or 250 mg/kg of [A-$^{14}$C]OK-5101 (lot no. CFQ12735, specific activity: 1.37 GBq/mmol, radiochemical purity: 99.2%) or 3 or 250 mg/kg of [B-$^{14}$C]OK-5101 (lot no. CFQ12736, specific activity: 1.37 GBq/mmol, radiochemical purity: 98.1%). Unlabeled OK-5101 technical (lot no. 01E1, purity: 98.46%) was used to adjust the specific activity of the dosing preparations. Urine and feces were collected at specified intervals up to 72 hours post-dose. The urine was the primary route of excretion for the 3 mg/kg treatment levels with 59 to 70% of the administered dose recovered by 72 hours. Recovery ranged from 25 to 33% in the feces. For the 250 mg/kg treatment groups, the sites of recovery were reversed with 68 to 80% of the administered radiolabel isolated in the feces and 15 to 27% of the radiolabel found in the urine. For the 3 mg/kg groups, 72 to 85% of the administered dose was excreted by 24 hours post-dose. For the 250 mg/kg groups, the 24-hour excretion ranged from 69 to 81% of the dose. After 72-hours, the tissue levels ranged from 0.9 to 2.5% of the administered dose for the 3 mg/kg groups and from 0.4 to 0.8% of the dose for the 250 mg/kg groups. The liver and kidneys were the primary sites of sequestration. Position of the radiolabel on the molecule did not apparently affect the excretion profile. There was no significant difference in the excretion profile or the tissue distribution of the radiolabel between the sexes. **Study supplemental** (study limited to excretion balance and tissue distribution characterizations). (Moore, 8/1/12)

53174-0056; 264927; " [Tolyl-U-$^{14}$C]-OK-5101: Excretion and Tissue Distribution in the Rat"; (T. Hardwick; Covance Laboratories Ltd., Harrogate, North Yorkshire HG3 IPY, England; Study No. 2554/036; 6/6/08); Twenty Fischer 344 female rats were dosed orally by gavage with 3 mg/kg/day of [Tolyl-U-$^{14}$C]-OK-5101( Code: CFQ14971 batch 1; specific activity: 3.454 MBq/mg; radiochemical purity: 97.9%) for up to14 days. Unlabeled OK-5101 technical (batch no. 5J01, purity: 99.9%) was used to adjust the specific activity of the dosing preparations. Four animals per time point were euthanized at 24 hours after the 4$^{th}$ and 7$^{th}$ doses and at 2, 24 and 72 hours post final dose. The distribution of radioactivity in the tissues was determined at each of these time points. Urine and feces were collected at specified intervals from 0 to 72 hours post-final dose. At 0 to 72 hours post-final dose, radioactivity in the urine and feces constituted 64 and 59% of the final administered dose and 4.5 and 4.2% of the total administered dose, respectively. The primary sites of recovery in the tissues were the kidneys and liver with the level of radioactivity gradually increasing over the course of the treatment period. By 72 hours post-final dose, the levels of radioactivity in the liver and kidneys had diminished to 3.8 and 5.4%, respectively, of the levels observed at 2 hours post-final dose. The level of radioactivity in the gastrointestinal tract largely reflected the passage of the dosing material through the gut. **Study supplemental** (study limited to excretion balance and tissue distribution characterizations using a multiple dosing regimen). (Moore, 8/13/12)

53174-0056; 264928; "$^{14}$C-BAS 9210 I (Cyflumetofen) - Study on the Plasmakinetics in Mice (Including Amendment No. 1)"; (E. Fabian, R. Landsiedel; Experimental Toxicology and Ecology, BASF SE, 67056 Ludwigshafen/Rhein, Germany; Study ID No. 02B0136/10B003; 9/30/11, amended, 10/26/11); Thirty CD1 mice/sex/group were dosed orally by gavage with 50, 250, 500 or 1000 mg/kg of $^{14}$C-BAS 9210 I (Cyflumetofen technical) (batch no. 975-1021, radiochemical purity: 98.8%, specific activity: 5.69 MBq/mg). Non-labeled BAS 9210 I (Cyflumetofen technical) (batch no. 01H1, purity: 97.08%) was used to maintain the specific activity of the dosing preparations between 0.5 and 2 MBq. The test material was rapidly absorbed with the tmax for the males being 30 minutes. For the females, plasma levels demonstrated a biphasic phenomenon with two Tmax values, one at 30 minutes or 1 hour and another at 2 or 8 hours post-dose. The females had a higher level absorption over the course of the 96-hour sample collection period based on the Cmax and AUC values. Reabsorption via the entero-hepatic recirculation process apparently contributed to these higher plasma levels. Two elimination T1/2 values were evident for both sexes with the initial half time values ranging from 0.7 to 2.82 hours irrespective of the dosing level. The terminal elimination T1/2 values ranged from 22 to 60 hours, likewise, irrespective of dosing level. **Study supplemental** (study included only an assessment of the pharmacokinetics). (Moore, 8/15/12)

53174-0052; 264920; "[$^{14}$C] OK-5101 (Phenyl-ring U and Tolyl-ring-U-Label): Metabolic Fate in Rats (Preliminary)"; (H. Nakamura; The Institute of Environmental Toxicology, Mitsukaido-shi, Ibaraki 303-00432, Japan; Study ID No. IET 02-8002; 7/14/04); Two Fischer 344 rat/sex/group were orally dosed with 3 or 250 mg/kg of [A-$^{14}$C]OK-5101 (lot no. CFQ12735, specific activity: 1.37 GBq/mmol, radiochemical purity: 99.2%) or 3 or 250 mg/kg of [B-$^{14}$C]OK-5101 (lot no. CFQ12736, specific activity: 1.37 GBq/mmol, radiochemical purity: 98.1%) in aqueous 3% hydroxypropyl cellulose. Unlabeled OK-5101 technical (lot no. 01E1, purity: 98.46%) was used to adjust the specific activity of the dosing preparations. One

animal/sex/group was included in either the pharmacokinetic or the mass balance studies. In the pharmacokinetic study, blood samples were drawn periodically between 0.5 to 72 hours post-dose. In the mass balance study, urine, feces and carbon dioxide were collected up to 72 hours post-dose and a tissue distribution evaluation was performed at 72 hours post-dose. Overall, the position of the radiolabel did not significantly affect the various parameters. There also was no apparent difference between the sexes. In the pharmacokinetic study, the time to tmax ranged from 0.5 to 1.0 hours for the 3 mg/kg treatments and from 1.0 to 4.0 hours for the 250 mg/kg treatments. Cmax ranged from 0.81 to 2.9 mg equivalents/L for the 3 mg/kg groups and from 12.49 to 29.82 mg equivalents/L for the 250 mg/kg groups. The t1/2 for the beta-phase of elimination ranged from 12 to 16 hours for the 3 mg/kg treatments and from 11.3 to 20 hours for the 250 mg/kg treatments. For the mass balance evaluation, the urine was the primary route of excretion for the 3 mg/kg treatment levels with 60 to 71% of the administered dose recovered by 72 hours. Recovery ranged from 24 to 36% in the feces. For the 250 mg/kg treatment groups, the sites of recovery were reversed with 69 to 81% of the administered radiolabel isolated in the feces and 13 to 25% of the radiolabel found in the urine. For the 3 mg/kg groups, 77 to 79% of the administered dose was excreted by 24 hours post-dose. For the 250 mg/kg groups, the 24-hour excretion ranged from 72 to 88% of the dose. After 72-hours the tissue levels ranged from 0.67 to 2.12% of the administered dose for the 3 mg/kg groups and from 0.26 to 0.72% of the dose for the 250 mg/kg groups. The liver and kidneys were the primary sites of sequestration. **Study supplemental** (performed as a preliminary study). (Moore, 7/27/12)

Collectively, the data from the above studies satisfy current requirements for an acceptable animal metabolism study.

## GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT

### Acute oral toxicity, rat

0034, 264879; "OK-5101 Technical- Acute Oral Toxicity to the Rat (Fixed Dose Method)" (Moore, E.L., Huntingdon Life Sciences Ltd., Huntingdon, Cambridgeshire, England, Study Identification Numbers(s) OSK 042/033030/AC OSK/042, 06/19/2003). 870.11. OK-5101 Technical (Lot No. 01H1, purity = 98.0%), prepared in water with 5% Gum Arabic and 4% Tween 80, was administered in a single dose by gavage to 5 female Han Wistar rats at a dose level of 2000 mg/kg. No mortalities occurred. Loose feces were observed in one treated animal beginning approximately 5 hours after treatment, clearing completely by day 2. Necropsy revealed no abnormalities. $LD_{50}$ (F) > 2000 mg/kg. NOEL (F) < 2000 mg/kg (based on loose feces). Toxicity Category III. **Acceptable**. (Corlett, 06/19/2012)

### Acute dermal toxicity

0034, 264880; "OK-5101l- Acute Dermal Toxicity to the Rat" (Moore, E.L., Huntingdon Life Sciences Ltd., Huntingdon, Cambridgeshire, England, Study Identification Numbers(s) OSK 032/032075/AC OSK/032, 06/10/2003). 870.12. OK-5101 (Lot No. 01H1, purity = 98.0%), prepared in 1% w/v aqueous methylcellulose, was applied to the clipped dorso-lumbar region of 5 Han Wistar rats per sex per dose at a dose level of 5000 mg/kg for 24 hours, covered with porous gauze held in place with a non-irritating, waterproof dressing. No mortalities occurred. No clinical signs and no signs of dermal irritation were observed. Necropsy revealed no

abnormalities. $LD_{50}$ (M/F) > 5000 mg/kg. Toxicity Category IV. **Acceptable**. (Corlett, 06/20/2012)

## Acute inhalation toxicity, rat

0034, 264881, 264882; "OK-5101- Acute (Four-hour) Inhalation Study in Rats" (Bowden, A.M., Huntingdon Life Sciences Ltd., Huntingdon, Cambridgeshire, England, Study Identification Numbers(s) OSK 031/024380, 06/23/2003). 870.13. OK-5101 (Lot No. 01H1, purity = 98.0%) was aerosolized and administered in a nose-only manner to 5 Wistar Han WI (Glx/BRL/Han) BR rats per sex per dose at a dose level (mean gravimetric and maximum practicable concentration) of 2.65 mg/l (mean MMAD (GSD) of 5.0 (2.61 um) for 4 continuous hours. No mortalities occurred. Exaggerated breathing, brown staining around snout/jaws, and fur/skin soiled with excreta were observed in both sexes after exposure with all signs clearing in all animals by day 2 of the 14-day observation period. Necropsy revealed no abnormalities. $LC_{50}$ (M/F) > 2.65 mg/l. Toxicity Category IV. **Acceptable**. (Corlett, 06/21/2012)

## Primary eye irritation, rabbit

0034, 264883; "OK-5101- Eye Irritation to the Rabbit (Including Amendment 1 and Amendment 2)" (Rees, P.B., Huntingdon Life Sciences Ltd., Huntingdon, Cambridgeshire, England, Study Identification Numbers(s) OSK 033/032629, revised final report date 02/08/2005). 870.24. 0.1 ml volume (approximately 92 mg) of OK-5101 (Lot No. 01H1, purity = 98.0%) was instilled into the lower everted eyelid of one eye of each of 3 New Zealand White rabbits. No corneal opacity or iritis was observed in any treated eye. Conjunctival irritation (redness, grade 2 in 1 treated eye and grade 1 in 1 treated eye) was observed 24 hours after treatment, with grade 1 redness observed in the 3 treated eyes 8 days after treatment and in 1 treated eye 15 days after treatment with all signs of irritation clearing in all treated eyes 22 days after treatment. Toxicity Category III. **Acceptable**. (Corlett, 06/25/2012)

## Primary dermal irritation

0034, 264884; "OK-5101- Skin Irritation to the Rabbit" (Rees, P.B., Huntingdon Life Sciences Ltd., Huntingdon, Cambridgeshire, England, Study Identification Numbers(s) OSK 034/032338, 07/03/2003). 870.25. Approximately 0.5 g of OK-5101 (Lot No. 01H1, purity = 98.0%) was applied to the skin of 3 New Zealand White rabbits clipped of hair in the dorso-lumbar region "wetted" with 0.5 ml of reverse osmosis water under a semi-occlusive dressing for 4 hours. No erythema or edema was observed at any treated test site at any time during a 72-hour observation period. Toxicity Category not determined. **Unacceptable but possibly upgradable** with the submission of documentation demonstrating that the application of the test material onto "wetted" skin sufficiently moistened the test material to ensure good contact with the skin. (Corlett, 06/25/2012)

## Dermal sensitization

0034, 264885; "Assessment of Contact Hypersensitivity to OK-5101 in the Albino Guinea Pig (Maximisation -Test)" (Hooiveld, M.J.J., Notox B.V., Hertogenbosch, The Netherlands, NOTOX project 376829, 07/16/2003). 870.26. The Magnusson and Kligman maximization assay was used to assess the potential of OK-5101 (Lot No. 01H1, purity = 98.0%) to elicit delayed contact hypersensitivity in the guinea pig. 10 Dunkin Hartley albino guinea pigs were treated with the test material at induction (intradermal injections followed by a topical application 1 week later) and at challenge (a topical application 13 days after the topical

induction). A concurrent negative control group consisting of a group of 5 animals was also included in the study; these animals were treated identically to the treated animals, except that during induction, the test material was replaced with the vehicle (corn oil). The challenge sites were examined 24 and 48 hours after removal of the patches. All treated animals exhibited moderate and confluent erythema or moderate erythema and edema at the challenge site. **The results of the study indicate that the test material is a sensitizer when using the Magnusson and Kligman maximization assay.** (Corlett, 06/27/2012)

## SUBCHRONIC STUDIES

### Oral toxicity, rodent†**:

****53174-0040 264900** Yoshida, T., "OK-5101: Repeated dose 90-day oral toxicity study in rats," The Institute of Environmental Toxicology, Ibaraki, Japan, 6/17/04. BASF # OTSA-0014(EN)-FR. Groups of 10 Fischer (F344/DuCrj) /sex/group were dosed in diet with OK-5101(cyflumetofen), purity 97.67%, Lot # 01D1, at 0, 100, 300, 1000, or 3000 ppm for 90 days. Achieved cyflumetofen dose levels were 5.4, 16.5, 54, and 167 mg/kg/day in treated males, and 6.3, 19.0, 63, and 193 mg/kg/day in females. NOEL = 300 ppm, based primarily on diffuse vacuolation the adrenal cortex in both sexes. Vacuolation of ovarian interstitial glands was observed in most high dose females, and the single case in a 1000 ppm female should be attributed to treatment. Liver absolute weights were markedly elevated at 3000 ppm in males, and relative liver weights were elevated in 1000 ppm males and in 3000 ppm females. Acceptable, with diffuse vacuolation the adrenal cortex as a "possible adverse effect." Aldous, 5/30/12.

53174-0059 264937 Buesen, R., "Summary report - BAS 9210 I (Cyflumetofen) - test study in Wistar rats - administration via the diet for 26 days," BASF SE, Ludwigshafen, Germany, 3/18/10. BASF Registration Document No. 2010/1034048. Groups of 5 rats/sex/group were dosed in diet for 26 days with presumed technical cyflumetofen in a supplementary (non-GLP, non-guideline) study at 0, 500, 1500, 4000, or 12000 ppm. Achieved dose levels were 43, 128, 339, and 1028 mg/kg/day in increasing male dose groups, and 46, 132, 351, and 1039 mg/kg/day in females. Apparent NOEL = 500 ppm (adrenocortical cytoplasmic vacuolation, macrovesicular, in 3/5 of each sex at 1500 ppm, and in all rats at higher dose levels). Adrenal cortex was grossly discolored in 3/5 1500 ppm females, and in all rats at higher dosages. Adrenal weights were statistically elevated in all female treatment groups (concurrent male NOEL = 1500 ppm). This was not consistent with findings with Wistar rats [N = 10/sex/sacrifice interval] in the chronic rat study with interim sacrifice groups at 4 weeks and 13 weeks (Record No. 264905). That study indicated a NOEL of 500 ppm at 4 weeks (LOEL of 1500 ppm) for adrenal weights in females, and a NOEL of 1500 ppm for female adrenal weights at 13 weeks. Further, the 13-wk rat subchronic study (Record No. 264900) found a 13-wk NOEL for adrenal weights in females to be 1000 ppm [LOEL = 3000 ppm]. Common findings at ≥ 4000 ppm in the present study included centrilobular hepatocellular hypertrophy in all males at ≥ 4000 ppm and in 1 and 3 females at 4000 and 12000 ppm, respectively; and vacuolation of ovarian luteal cells. Useful supplementary data. Aldous, 5/31/12.

53174-0039, 264898; “OK-5101: Repeated Dose 28-Day Toxicity Study in Rats” (Yoshida, T., The Institute of Environmental Toxicology, Ibaraki, Japan, Study Identification Number(s) IET 01-0031, 06/14/2004). 870.3050. OK-5101 (Lot No. 01C1, purity = 99.3%) was admixed to the diet and fed to 6 Fischer (F344/DuCrj) rats per sex per dose at dose levels of 0 (untreated diet), 100, 500, 1000, or 5000 ppm (0, 7.50, 37.6, 75.1, and 384 mg/kg/day, respectively for males and 0, 8.05, 40.8, 79.8, and 409 mg/kg/day, respectively for females) for 4 weeks. No animals died during the study. No treatment-related clinical signs were observed. No treatment-related effects on body weight or food consumption were observed. Hematological investigations revealed no treatment-related effects. Blood biochemistry investigations revealed a treatment-related increase in the mean blood urea nitrogen level (in males at 5000 ppm) and treatment-related decreases in mean total cholesterol (in males at 1000 and 5000 ppm, in females at 5000 ppm), and mean triglyceride (in males at 1000 and 5000 ppm) levels. Urinalysis revealed a treated-related increase in ketones in females at 5000 ppm. Treatment-related increases in mean relative liver weight (in males at 1000 and 5000 ppm, in females at 5000 ppm), in mean relative kidney weight (in both sexes at 5000 ppm), and in mean relative adrenal weight (in males at 5000 ppm, in females at 1000 and 5000 ppm) were observed. Macroscopic examination revealed a treatment-related increase in adrenals white in color and exhibiting hypertrophy in both sexes at 5000 ppm. Microscopic examination revealed treatment-related increases in diffuse hypertrophy of the hepatocytes (in males at 1000 and 5000 ppm, in females at 1000 ppm), diffuse vacuolation of the cortical cells in the adrenals (in both sexes at 1000 and 5000 ppm), diffuse hypertrophy of the cortical cells in the adrenals (in females at 1000 and 5000 ppm), and vacuolation of the interstitial cells in the ovaries at 5000 ppm. **No adverse effects.** NOEL (M) = 37.6 mg/kg/day (500 ppm) and NOEL (F) = 40.8 mg/kg/day (500 ppm) based on increased relative liver and adrenal weights and liver and adrenal histopathology. **Acceptable.** (Corlett and Leung, 07/05/2012)

53174-0039, 264899; “OK-5101: Repeated Dose 28-Day Toxicity Study in Mice” (Yoshida, T., The Institute of Environmental Toxicology, Ibaraki, Japan, Study Identification Number(s) IET 01-0078, 06/17/2004). 870.3050. OK-5101 (Lot No. 01D1, purity = 97.67%) was admixed to the diet and fed to 6 SPF ICR mice (Crj:CD-1) per sex per dose at dose levels of 0 (untreated diet), 100, 500, 1000, or 5000 ppm (0, 13.1, 67.2, 135, and 663 mg/kg/day, respectively for males and 0, 14.5, 74.9, 150, and 763 mg/kg/day, respectively for females) continuously for 4 weeks. No animals died during the study. No treatment-related clinical signs were observed. No treatment-related effects on body weight or food consumption were observed. Hematological and blood chemistry investigations revealed no treatment-related effects. No treatment-related effects on internal organ weights were observed. Macroscopic examination revealed no abnormalities. Microscopic examination revealed treatment-related increases in diffuse vacuolation of the cortical cells in the adrenals in females at 5000 ppm and in diffuse hypertrophy of the cortical cells in the adrenals in both sexes at 5000 ppm. **No adverse effects.** NOEL (M) = 135 mg/kg/day (1000 ppm) and NOEL (F) = 150 mg/kg/day (1000 ppm) based on adrenal gland histopathology. **Acceptable.** (Corlett and Leung, 07/06/2012)

53174-0041, 264901; “OK-5101: Repeated Dose 90-Day Toxicity Study in Mice” (Yoshida, T., The Institute of Environmental Toxicology, Ibaraki, Japan, Study Identification Number(s) IET 01-0111, 06/21/2004). 870.3100. OK-5101 (Lot No. 01D1, purity = 97.67%) was admixed to the diet and fed to 10 (SPF) ICR mice (Crj:CD-1) per sex per dose at dose levels of 0

(untreated diet), 300, 1000, 3000, or 10000 ppm (0, 35.4, 117, 348, and 1200 mg/kg/day, respectively for males and 0, 45.0, 150, 447, and 1509 mg/kg/day, respectively for females) continuously for 13 weeks. No animals died during the study. No treatment-related clinical signs were observed. No treatment-related effects on body weight or food consumption were observed. Hematological and blood chemistry investigations revealed no treatment-related effects. No treatment-related effects on internal organ weights were observed. Macroscopic examination revealed treatment-related enlarged adrenals in males at 10000 ppm. Microscopic examination revealed treatment-related increases in diffuse vacuolation of the cortical cells in the adrenals in females at 3000 and 10000 ppm and in diffuse hypertrophy of the cortical cells in the adrenals in males at 3000 and 10000 ppm. **No adverse effects.** NOEL (M) = 117 mg/kg/day (1000 ppm) and NOEL (F) = 150 mg/kg/day (1000 ppm) based on adrenal gland histopathology. **Supplemental study** (no ophthalmology was performed)**.** (Corlett and Leung, 07/11/2012)

53174-0058; 264932; "OK-5101: Repeated Dose 2-Week Oral Toxicity Study in Rats"; (S. Sakai; Otsuko Chemical Co., Ltd., Naruto Research Center, Naruto, Tokushima 772-8601, Japan; Study No. 01A4; 4/11/01); Six Fischer 344 rats/sex/group received 0, 1000 or 10000 ppm of OK-5101 (Cyflumetofen technical) (lot no. HN0101004; purity: 98%) in the diet for 2 weeks ((M) 0, 101.1, 980.6 mg/kg/day, (F) 0, 104.6, 1000.4 mg/kg/day). No deaths resulted from the treatment. Perineal staining was noted for the females in the 10000 ppm group. The mean body weights and food consumption of the 10000 ppm females were less than the control values ($p<0.05$ or 0.01). In the clinical chemistry evaluation, serum albumin was increased for both sexes in the 10000 treatment group ($p<0.05$). The serum globulin level was lower for the 10000 ppm females. As a consequence, the albumin/globulin ratios were increased for both sexes in the 10000 ppm group ($p<0.01$). No treatment-related effect was noted in the urinalysis. In the necropsy examination, the mean absolute and relative thymus weights of the 10000 ppm males were less than the control values ($p<0.05$ or 0.01). The absolute and relative liver weights of both sexes in the 10000 ppm group and the relative liver weight of the 1000 ppm males were greater than the control values ($p<0.05$ or 0.01). The relative kidney weights of both sexes in the 10000 ppm group were greater than those of the control group ($p<0.05$ or 0.01). The absolute and relative adrenal weights of both sexes in the 10000 ppm group and the females in the 1000 ppm group were greater than the control values ($p<0.05$ or 0.01). The relative adrenal weights of the 1000 ppm males were greater than the control as well ($p<0.05$). In the histological examination, diffuse hypertrophy of the hepatocytes was noted in the livers of both sexes in the 10000 ppm group. Cortical cell vacuolation was evident in the adrenal glands of both sexes in the 1000 and 10000 ppm groups. Interstitial cell vacuolation was noted in the ovaries of the females in both the 1000 and 10000 ppm groups. Vacuolation of the corpora lutea was also evident in the ovaries of the 10000 ppm females. Target organ: adrenal gland. **No adverse effect indicated. Rat 2-Week Dietary Toxicity NOEL:** (M/F) < 1000 ppm ((M) < 101.1 mg/kg/day, (F) < 104.6 mg/kg/day) (based upon treatment-related effects on the adrenal glands of both sexes in the 1000 ppm treatment group); **Study supplemental** (non-guideline study). (Moore, 7/6/12)

## Oral toxicity, non-rodent**:

53174-0042, 264902; "90-Day Repeated Oral Dose Toxicity Study of OK-5101 in Beagle Dogs" (Nagashima, Y., Kannami Laboratory, Bozo Research Center Inc., Shizuoka, Japan, Study Identification Number(s) B-4857, 03/18/2003). 870.3150. OK-5101 (Lot No. 01H1, purity = 98.4%) was administered via gelatin capsules to 4 beagle dogs per sex per dose at dose

levels of 0 (empty capsules), 30, 300, or 1000 mg/kg/day daily for 90 days (males) or 91 days (females). No mortalities occurred. No dose-related or treatment-related clinical signs were observed. A treatment-related decrease in mean body weight gain was observed in both sexes at 1000 mg/kg/day. No treatment-related effects on food consumption were observed. Urinalysis, and hematological and blood chemistry investigations revealed no treatment-related effects. A treatment-related increase in mean relative adrenal gland weight was observed in both sexes at 1000 mg/kg/day. Macroscopic examination revealed treatment-related enlarged adrenals in one male at 1000 mg/kg/day. Microscopic examination revealed a treatment-related increase in vacuolation of the cortical cells in the zona fasciculata, the zona glomerulosa, and the zona reticularis of the adrenal glands in both sexes at 1000 mg/kg/day. **No adverse effects.** NOEL (M/F) = 300 mg/kg/day based on decreased mean body weight gain, increased mean relative adrenal gland weight, and increased vacuolation of the cortical cells in the zona fasciculata, the zona glomerulosa, and the zona reticularis of the adrenal glands. **Acceptable.** (Corlett and Leung, 07/20/2012)

53174-0059 264934 "28-day repeated oral dose toxicity study of OK-5101 in beagle dogs," Kannami Laboratory, Bozo Research Center Inc., Shizuoka, Japan, 3/18/2003. Laboratory Study # B-4833. Groups of 3 dogs/sex/group were dosed by capsule with OK-5101 (Lot No. 01H1, purity = 98.4%) for 4 weeks at 0, 100, 300, or 1000 mg/kg/day in a range-finding study for the subsequent 3-month subchronic study. NOEL = 100 mg/kg/day, based primarily on fine vacuolation in adrenal cortical zona fasciculata and zona reticularis. Fine vacuolation of the zona glomerulosa was also elicited in some 300-1000 mg/kg/day males, and at 1000 mg/kg/day in females. Clinical signs of "feces mixed with test substance" at 300 and particularly at 1000 mg/kg/day suggested incomplete absorption of test article. Useful supplementary data. No adverse effects indicated. Results support dose selection for the subchronic study. Aldous, Jan. 9, 2013.

## Dermal toxicity, 21/28-day or 90-day**:

**53174-0043; 264904; "BAS 9210 I (Cyflumetofen)- Repeated Dose 28-day Dermal Toxicity Study in Wistar Rats" (Buesen et al., Experimental Toxicology and Ecology, BASF SE, Ludwigshafen, Germany, Study Identification Number(s) 33C0510/09S003 350766, 11/11/2010). 870.3200. BAS 9210 I (Cyflumetofen) (Batch Identification 01H1, purity = 98.4%), suspended in 1% aqueous carboxymethylcellulose, was applied to the clipped dorsal skin of 10 Crl:WI(HAN) rats per sex per dose at dose levels of 0 (vehicle only), 100, 300, or 1000 mg/kg/day for 6 hours, 5 days per week, for 4 weeks using a semi-occlusive dressing. No mortalities occurred. Clinical observations (conducted daily) and detailed clinical observations (conducted weekly) revealed no treatment-related abnormalities. FOB and motor activity assessments conducted at the end of the treatment period revealed no treatment-related effects. No treatment-related effects on mean body weight or mean food consumption were observed. Hematology and serum chemistry investigations revealed no treatment-related effects. No toxicological effects on organ weights were observed. Macroscopic and histopathological examinations revealed no treatment-related abnormalities. **No adverse effects.** NOEL (M/F, systemic and skin) = 1000 mg/kg/day (based on no effects at the highest dose tested). **Acceptable**. (Corlett and Leung, 08/02/2012)

## CHRONIC STUDIES

### Chronic, rat **

**53174-0044 264905 Yoshida, T., "OK-5101: Repeated dose 1-year oral toxicity study in rats," The Institute of Environmental Toxicology, Ibaraki, Japan, 6/22/04. BASF # OTSA-0045(EN)-FR. Groups of 10 Fischer (F344/DuCrj) /sex/group were dosed in diet with OK-5101 (cyflumetofen), purity 97.67%, Lot # 01D1, for 4, 13, or 26 weeks. Groups of 20/sex were dosed for 52 weeks. Mean cyflumetofen intake in treated groups was 1.9, 5.6, 19, and 57 mg/kg/day in increasing male dose groups, and 2.3, 6.9, 23, and 69 mg/kg/day in females. Investigators assessed chronic study parameters including scored FOB parameters in the home cage, during handling, and in the open field during weekly clinical examinations, and grip strength and sensorimotor responses, along with motor activity evaluation, at 49 weeks. NOEL (M/F) = 500 ppm, based on adrenal gland diffuse cortical cell hypertrophy in all high dose females, adrenal gland diffuse cortical cell vacuolation in most high dose males, diffuse hepatocellular hypertrophy in 3/10 high dose males at 4 weeks only, and vacuolation of ovarian interstitial glands in a total of 8/40 high dose females between 13 and 52 week sacrifices. There were no other definitive effects. Acceptable, with no adverse effects. Aldous, Oct. 8, 2012.

### Chronic, dog **

**53174-0042, 264903; "1-Year Repeated Dose Toxicity Study of OK-5101 in Beagle Dogs (Including Amendment No. 1 and Amendment No. 2)" (Nagashima, Y., Kannami Laboratory, Bozo Research Center Inc., Shizuoka, Japan, Study Identification Number(s) B-4858, 01/31/2008). 870.4100. OK-5101 (Lot No. 01H1, purity = 98.4%) was administered via gelatin capsules to 4 beagle dogs per sex per dose at dose levels of 0 (empty capsules), 30, 300, or 1000 mg/kg/day daily for 364 days (males) or 365 days (females). No mortalities occurred. No treatment-related clinical signs were observed. No treatment-related effects on body weight or food consumption were observed. Urinalysis and hematological investigations revealed no treatment-related effects. A treatment-related decrease in the mean triglycerides levels was observed in both sexes at 1000 mg/kg/day. A treatment-related increase in mean relative adrenal gland weight was observed in both sexes at 1000 mg/kg/day. Macroscopic examination revealed treatment-related enlarged adrenals in one male at 1000 mg/kg/day, in one female at 300 mg/kg/day, and in all females at 1000 mg/kg/day. Microscopic examination revealed a treatment-related increase in vacuolation of the cortical cells in the zona fasciculata, the zona glomerulosa, and the zona reticularis of the adrenal glands along with degeneration of the cortical cells in both sexes at 300 and 1000 mg/kg/day. **No adverse effects.** NOEL (M/F) = 30 mg/kg/day based on increased vacuolation of the cortical cells in the zona fasciculata, the zona glomerulosa, and the zona reticularis of the adrenal glands along with degeneration of cortical cells in the zona fasciculata and zona reticularis. **Acceptable.** (Corlett and Leung, 07/25/2012)

### Oncogenicity, rat **

**53174-0045 264906 Yoshida, T., "OK-5101: carcinogenicity study in rats," The Institute of Environmental Toxicology, Ibaraki, Japan, 7/29/04. BASF # OTSA-0046(EN)-FR. Groups of 50 Fischer (F344/DuCrj) rats/sex/group were dosed in diet with OK-5101 (cyflumetofen), purity 97.67%, Lot No. 01D1, for 104 weeks in an oncogenicity study at 0, 150, 500, or 500 ppm. Mean cyflumetofen intake in treated groups was 4.9, 16.5, and 50 mg/kg/day in increasing male dose groups, and 6.1, 20.3 and 62 mg/kg/day in females. Cyflumetofen was not oncogenic.

Chronic NOEL = 500 ppm in both sexes (M: 16.5 mg/kg/day, F: 20.3 mg/kg/day). Adrenal cortical cell hypertrophy incidence was sharply elevated in both sexes at 1500 ppm, with no change at 500 ppm. Luminal dilatation in the uterine horn was plausibly treatment-related at 1500 ppm. Reduction of aging effects of testes (interstitial cell hyperplasia and seminiferous tubule atrophy) was evidently treatment-related, but not adverse. Acceptable, with no adverse effects. Aldous, 11/29/12.

### Oncogenicity, mouse**

**53174-0046 264907 Yoshida, T., "OK-5101: carcinogenicity study in mice," The Institute of Environmental Toxicology, Ibaraki, Japan, 7/27/04. BASF # OTSA-0046(EN)-FR. Groups of 52 Crj:CD-1 mice/sex/group were dosed in diet with OK-5101 (cyflumetofen), purity 97.67%, Lot No. 01D1 for 78 weeks at 0, 150, 500, 1500, or 5000 ppm, for mean estimated doses of 15.5, 54, 156, or 537 mg/kg/day for corresponding treated males, and 14.3, 48, 144, or 483 mg/kg/day for females. NOEL = 1500 ppm, based on diffuse vacuolation in adrenal cortical cells, significantly elevated at 5000 ppm in both sexes. Treatment did not elicit tumors, nor were other treatment effects evident. Acceptable, with no adverse effects. Aldous, July 6, 2012.

## GENOTOXICITY

**Gene Mutation overall assessment:** The bacterial reverse mutation test (below, Record No. 264914) was negative at all dose levels, up to the limit test of 5000 µg/plate. In that study, precipitation occurred at 5000 µg/plate without S-9 activation, but no cytotoxicity was observed up to 5000 µg/plate with or without S-9. In the L5178Y mouse lymphoma cell assay (Record No. 264915), increased mutagenicity was strictly limited to levels which were cytotoxic and/or levels which caused precipitation. Closely-spaced concentrations below the cytotoxic range did not show increased mutagenicity. The mouse lymphoma cell assay found the strongest response to be an increase in small colonies, taken by investigators to suggest mainly chromosome aberrations. Two independent *in vitro* chromosome aberration studies (below) were acceptable and negative, as well as DNA damage studies which follow. The rat and mouse oncogenicity studies were negative. Thus the above mouse lymphoma cell assay responses, although clearly showing mutation frequency responses at the higher concentrations, are most consistent with a threshold response. Aldous, Jan. 10, 2013.

### Bacterial reverse mutation assay**

** 53174-0052; 264914; "OK-5101: Bacterial Reverse Mutation Test"; (K. Matsumoto; The Institute of Environmental Toxicology, Mitsukaido-shi, Ibaraki 303-00432, Japan; Project ID No. IET 01-0033; 8/6/01); *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and *E. coli* strain WP2 *uvr*A were treated for 48 hours at 37$^{o}$ C with OK-5101 (Cyflumetofen technical) (lot no. 01D1; purity: 97.67%) at concentrations ranging from 20.6 to 5000 µg/plate (+/-) activation in the 1$^{st}$ trial and from 156 to 5000 µg/plate (+/-) activation in the 2$^{nd}$ trial. Each treatment level was plated in triplicate. An S9 fraction derived from the livers of rats pre-treated with phenobarbital and/or 5,6-benzoflavone for 4 days was used to metabolize the test material. There was no increase in the incidence of reverse mutation for any of the strains under conditions of (+/-) activation in either trial. **No adverse effect indicated.** Positive controls were functional. **Study acceptable.** (Moore, 7/18/12)

## Mutagenicity: *In vitro* mammalian cell assay†**

**** 53174-0052; 264915**; "Evaluation of the Mutagenic Activity of OK-5101 in an *In Vitro* Mammalian Cell Gene Mutation Test with L5178Y Mouse Lymphoma Cells"; (C.M. Verspeek-Rip; Notox B.V., 5231 DD's - Hertogenbosch, The Netherlands; Project ID No. 485622; 11/6/07); Mouse lymphoma L5178Y cells (clone 3.7.2C ($TK^{+/-}$)) were treated with OK-5101 (Cyflumetofen technical) (batch no. 01H1; purity: 98.4%) at concentrations ranging from 20 to 90 µg/ml under conditions of non-activation and from 10 to 140 µg/ml under conditions of activation for 3 hours at $37^{o}$ C. The vehicle control samples were incubated in duplicate. Single cultures were performed for each treatment level. An S9 fraction derived from the livers of rats pre-treated with phenobarbital/B-naphthoflavone was used to metabolize the test material. The size of the mutant colonies was reported as a bimodal distribution. There was treatment-related increase in the mutation frequency under conditions of both non-activation and activation. The positive controls were functional. **Possible adverse effect indicated. Study acceptable.** (Moore, 7/19/12)

## Mutagenicity: *In vivo* cytogenetics**

** 53174-0052; 264918; "OK-5101: Micronucleus Test in Mice"; (K. Matsumoto; The Institute of Environmental Toxicology, Mitsukaido-shi, Ibaraki 303-00432, Japan; Study ID No. IET 01-0035; 12/16/03); Five Crl:CD-1 (ICR) male mice/group were dosed orally twice in a 24-hour interval by gavage with 0 (vehicle: aqueous 0.5% carboxymethylcellulose), 500, 1000, or 2000 mg/kg/day of OK-5101 (Cyflumetofen technical) (lot no. 01D1; purity: 97.67%). All of the animals were euthanized at 24 hours post-final dose. A positive control group of 5 animals were treated by oral gavage with mitomycin C, 10 mg/kg (one dose) and was euthanized at 24 hours post-dose. Bone marrow samples from the femur were examined, The percentage of polychromatic erythrocytes PCE with a micronucleus and the percentage of PCE to the total number of erythrocytes were determined. No treatment-related increase in the percentage of PCE's with a micronucleus was noted. The percentage of PCE to total erythrocytes was not significantly affected as well. The positive control was functional. **No adverse effect indicated. Study acceptable.** (Moore, 7/25/12)

** 53174-0052; 264919; "Evaluation of DNA Repair Inducing Ability of OK-5101 in Male Rat Hepatocytes (*In Vivo* Rat Hepatocyte DNA-Repair Assay)"; (C.A.F. Buskens; Notox B.V., 5231 DD's - Hertogenbosch, The Netherlands; Study ID No. 486284; 10/30/07); Six male Wistar rats/group were dosed orally by gavage with 1000 or 2000 mg/kg of OK-5101 (Cyflumetofen technical) (Batch No. 01H1; purity: 98.4%). Two animals were dosed with the vehicle, corn oil, and one animal each was dosed with dimethylnitrosamine (DMN), 10 mg/kg, or 2-acetylaminofluorene (2-AAF), 50 mg/kg, as positive controls. Three animals/group in the treatment groups and 1 animal in the vehicle control group and the DMN positive control animal were euthanized at 2-4 hours post-dose. The 3 remaining animals/group in the treatment groups, the remaining vehicle control animal and the 2-AAF positive control animal were euthanized at 12-16 hours post-dose. Hepatocytes were isolated and viability was determined by trypan blue dye exclusion. After attachment, cells were exposed to (methyl-$^{3}$H) thymidine for 4 hours followed by an overnight incubation with unlabeled thymidine. One hundred cells were scored

per animal. No increase in the net nuclear grain counts was evident at any dose level or sampling time. **No adverse effect indicated**. The positive control was functional. **Study Acceptable**. (Moore, 7/26/12).

### Chromosome effects**

** 53174-0052; 264916; "OK-5101: *In Vitro* Mammalian Chromosome Aberration Test"; (K. Matsumoto; The Institute of Environmental Toxicology, Mitsukaido-shi, Ibaraki 303-00432, Japan; Study ID No. IET 01-0034; 12/15/03); Chinese hamster lung cell cultures were treated with concentrations of OK-5101 (Cyflumetofen technical) (lot no. 01D1; purity: 97.67%) ranging from 25 to 200 µg/ml under conditions of (+) activation and from 6.25 to 50 µg/ml under conditions of (-) activation. The cells were exposed to the test material for 6 hours, followed by an additional 18 hours of incubation. In addition, the cells were exposed to concentrations of the test material ranging from 3.75 to 30 µg/ml for 24 or 48 hours without activation. A phenobarbital/5,6-benzoflavone-induced rat liver S9 fraction was used for activation. At least two cultures per treatment level were maintained. No treatment-related increase in number of cells with chromosomal or numerical aberrations (polyploidy) was evident. **No adverse effect indicated.** Positive controls were functional. **Study acceptable.** (Moore, 7/24/12)

** 53174-0052; 264917; "BAS 9210 I (Cyflumetofen): *In Vitro* Chromosome Aberration Assay in V79 Cells"; (M. Schulz, R. Landsiedel; Experimental Toxicology and Ecology, BASF SE, 67056 Ludwigshafen, Germany; Study ID No. 32M0510/094436; 1/25/11); V79 Chinese hamster cells were exposed to concentrations of BAS 9210 I (Cyflumetofen technical) (batch no. 01H1; purity: 97.08%) ranging from 10 to 160 µg/ml under conditions of activation and from 2.5 to 80 µg/ml under conditions of non-activation for 4 hours and incubated for an additional 14 hours in the 1$^{st}$ trial. In the 2$^{nd}$ trial, the non-activated cultures were exposed to the test material at concentrations ranging from 0.31 to 10 µg/ml for 4 hours and then were incubated for an additional 14 hours. In the 3$^{rd}$ trial, the activated cultures were exposed to concentrations of the test material ranging from 20 to 320 µg/ml for 4 hours and incubated for an additional 24 hours. The non-activated cultures were exposed to concentrations of the test material ranging from 0.31 to 40 µg/ml for 18 hours with no recovery period and from 2.5 to 40 µg/ml for 18 hours with a 10-hour recovery period. A phenobarbital/beta-naphthoflavone-induced rat liver S9 fraction was used to metabolize the test material. Duplicate cultures were performed at each treatment level. One hundred metaphases per culture were evaluated (200 metaphases per treatment level) (only 100 metaphases per treatment level for the positive control samples). There was no treatment-related increase in chromosomal cell aberrations under conditions of either activation or non-activation. Positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 7/25/12)

## REPRODUCTIVE TOXICITY, RAT**

**53174-0051 264913 Takahashi, K., "OK-5101: Reproductive toxicity study in rats," The Institute of Environmental Toxicology, Ibaraki, Japan, 7/23/04. BASF # OTSA-0059(EN)-FR. Groups of 24 Wistar rats/sex were dosed in diet with OK-5101 (Cyflumetofen), purity 97.67%, Lot No. 01D1 at 0, 150, 500, or 1500 ppm. Achieved dose levels during pre-mating were 10.4, 35, and 100 mg/kg/day in F0 males and 12.0, 40, and 122 mg/kg/day in F0 females (F1 mean dose levels were only marginally higher). Parental systemic toxicity NOEL = 150 ppm, based on

adrenal changes in 500 ppm females (grossly "white" or "enlarged," significantly elevated adrenal weights, and diffuse hypertrophy of zona glomerulosa). These findings were observed also in high dose males. A non-significant increase in diffuse hypertrophy in 500 ppm males is also plausibly treatment-related. Parental reproductive effects NOEL = 150 ppm, based on substantial reduction of circulating FSH in post-lactational F1 females at 500 and 1500 ppm. Circulating 17 β-estradiol was reduced in 1500 ppm F1 females. Ovarian interstitial cell vacuolation was elevated at 1500 ppm in F1 females. Estrous cycle length was marginally elevated in 1500 ppm F1 females, associated with increased incidences of 2 consecutive days of estrus or diestrus compared to other groups. There were no treatment-related effects on reproduction parameters. Post-lactational progesterone was statistically significantly reduced in all groups with a flat dose-response curve: this does not appear to be a critical finding (see discussion section). Offspring viability and growth NOEL = 500 ppm, based on pup body weight decrements (of 4-5 g at weaning). Pup general toxicity NOEL = 150 ppm. Pup adrenal weights at weaning were significantly reduced at 500 and 1500 ppm . Diffuse hypertrophy in adrenal zona glomerulosa and zona fasciculata was greatly elevated in 1500 ppm weanlings. Lesser increases in one or the other zone, sometimes statistically significant, were observed in either sex at 500 ppm, likely treatment-related. Female attainment of vaginal opening was delayed by 1.5 days at 1500 ppm. Female pup body weights at attainment were comparable to controls. Acceptable, with no adverse effects. Aldous, Dec. 11, 2012.

53174-0050 264912 Takahashi, K., (pilot study to the above reproduction study). Responses in this pilot study did not indicate NOEL's that were lower than the primary study. No DPR worksheet. Aldous, June 12, 2012.

## DEVELOPMENTAL TOXICITY

### Rat**

**53174-0048 264909 York, R. G., "Oral (gavage) developmental toxicity study of OK-5101 in rats," Argus Research, Horsham, PA, 12/19/01. BASF Registration No. OTSA-0012-FR. Groups of 25 mated Wistar Hannover GALAS dams were dosed by gavage on gestation days 6-19 with OK-5101 (cyflumetofen), purity 97.67%, Lot 01D1 (aq. suspension in 5% gum arabic with 0.4% Tween 80®) at 0, 50, 250, or 1000 mg/kg/day. Maternal NOEL = 50 mg/kg/day, based on slight adrenal weight increases and slight vacuolation of adrenal cortical cells at 250 mg/kg/day. Adrenal weights were significantly elevated and most 1000 mg/kg/day dams showed diffuse bilateral adrenal cortical cell hypertrophy and vacuolation. Developmental NOEL = 50 mg/kg/day, based on some evidence of ossification delays of sternal centra. Acceptable, with no adverse effects. Aldous, Nov. 1, 2012.

53174-0047 264908 (pilot study for 53174-0048 264909, above). Cited in that review, but no DPR worksheet is needed for this pilot. Aldous, 7/10/12.

### Rabbit**

**53174-0049 264911 York, R. G., "Oral (stomach tube) developmental toxicity study of OK-5101 in rabbits," Argus Research, Horsham, PA, 12/22/03. BASF Registration No. OTSA-0074. Groups of 25 NZW rabbits were dosed in an aqueous suspension with OK-5101 (cyflumetofen),

purity 97.67%, Lot 01D1, at 0, 50, 250, or 1000 mg/kg/day over gestation days 6-28. Maternal NOEL = 50 mg/kg/day (decreased food consumption and decreased liver weights at 250-1000 mg/kg/day). Developmental NOEL = 50 mg/kg/day (dose-response for ossification delay in xiphoid, and for a slight increase in pairs of ribs at the highest two dose levels, resulting in increased thoracic vertebrae and associated decreased lumbar vertebrae counts). Mean fetal weights at 1000 mg/kg/day were 13% lower than controls. Acceptable, with no adverse effects. Aldous, 7/27/12.

53174-0048 264910 Pilot study for 53174-0049 264911, above. This pilot indicated that dose levels up to the limit test of 1000 mg/kg/day could be administered in the primary study. No remarkable findings. No DPR worksheet. Aldous, 7/27/12.

## NEUROTOXICITY

53174-0036 264894 Kaspers, U. and B. van Ravenzwaay, "Positive control study concerning neurotoxicity in Wistar rats - single administration by gavage or subcutaneously," BASF, Ludwigshafen, Germany, March 2, 2009. BASF # 2009/7006730. Groups of 10 Wistar rats/sex/group were dosed with 30 mg/kg methylphenidate once by gavage, then 28 days later with diazepam (4 mg/kg) once by subcutaneous injection to the same animals. Investigators performed FOB's and motor activity evaluations at 30 min and at 2.5 hrs after each treatment. There were 10 controls/sex. Inter-observer FOB comparisons showed that negative controls rarely were scored to show the most characteristic responses. Positive controls showed expected responses, however some qualitative assessments like "gait impairment" and altered "activity/arousal level" often showed appreciable inter-observer variability. Common findings with methylphenidate included dilated pupils, poor adaptation of pupils to light, and slightly reduced foot splay in males. Diazepam was associated with reduced feces in males, reduced rearing in both sexes, decreased hindlimb grip strength in males, increased landing foot-splay in females, dilated pupils, slightly impaired coordination, and reduced exploratory behavior (the latter particularly in males). Reflex changes in diazepam rats included reduced adaptability to light, poor righting response, and absent response to pain stimulus. Motor activity found methylphenidate to show stimulation (elevated initial interval activity and delayed accommodation), whereas diazepam showed markedly depressed motor activity (greatly diminished initial interval activity, and rapid decline to low activity). Acceptable inter-observer consistency on FOB's, and appropriate findings for test articles. Data validate laboratory competency for FOB evaluations. Aldous, 6/15/12.

53174-0037 264896 Mellert, W., W. Kaufmann, and B. van Ravenzwaay, "Triethyltin bromide - Positive control study for neurotoxicity in Wistar rats - single intraperitoneal administration," BASF, Ludwigshafen, Germany, 4/28/08. BASF # 2008/7020382. Groups of ten Wistar rats/sex/group were dosed once ip with 0, 1, 3, or 5 mg/kg Triethyltin bromide, 97%, in 0.9% saline, at 5 ml/kg b.w. All received FOB and motor activity assessments at days -7, 0 (i.e. day of treatment), 7, and 14. Five rats/sex/group were sacrificed by perfusion and evaluated for neurohistopathology after 14 days. FOB and neurohistopathology were done blinded to treatment. FOB and motor activity effects were limited to Day 0. Common FOB home cage responses were rats lying on their abdomens or on their sides, or "unable to walk" (these findings in both sexes and with strong dose-responses from 1-5 mg/kg). "Eyelids half closed" were

observed in the two highest dose groups. Major open field responses were "On cage removal, shows no resistance to handling and seems indifferent to handling," and gait impairments ranging in degree from "unsteady gait" to "shuffling gait," to "dragging hindlimbs" (the latter limited to two 5 mg/kg males). Activity/arousal observations of "reduced exploration of area" showed dose-response over all treatment levels in both sexes. Sensori-motor changes such as impaired righting response and response on handling described as "very easy to handle, animal is limply hanging in the hand" were dose-related at 3-5 mg/kg. Two high dose females had non-reactive pupils (persistently contracted). Investigators found increased landing foot splay and decreased rearing counts in both sexes at 3-5 mg/kg. Fore-limb and hind-limb strength was significantly reduced in 3-5 mg/kg females, and hind-limb strength was reduced in 5 mg/kg males. Motor activity counts were strongly (dose-related) reduced in 3-5 mg/kg rats: counts were typically reduced in the first interval, and swiftly reduced to low baseline levels at later intervals. Motor activity was marginally reduced in 1 mg/kg males. Histopathology evaluations revealed "diffuse vacuolation of white matter" in 3 to 5 mg/kg males and females, with strong dose-response in incidence and degree, in the frontal lobe, parietal lobe, midbrain, pons, and cerebellum. Further, even the 1 mg/kg males and females showed "diffuse vacuolation of white matter" in the medulla oblongata and the cervical spinal cord. Results validated the capability of the laboratory to reproducibly identify the above parameters as treatment effects, and characterize this test article as a useful positive control. Valid positive control study. Aldous, 6/19/12.

## Acute neurotoxicity, rat**

**53174-0035 264886 Buesen, R., H. Marxfeld, E. Fabian, and B. van Ravenzwaay, "BAS 9210 I (cyflumetofen) - acute oral neurotoxicity study in Wistar rats - administration via gavage," BASF SE, Ludwigshafen, Germany, 12/15/10. BASF # 2010/1156035. Groups of 10 Wistar rats/sex/group were dosed once with 0, 125, 500, or 2000 mg/kg BAS 9210 I (cyflumetofen), purity 97.08%, Lot No. 01H1. Functional observational battery (FOB) and motor activity were conducted on days -7, 0, 7, and 14. Five rats/sex/group were designated for neurohistopathology, with controls and high dose rats examined initially. As there were no effects at the highest dose, intermediate groups were not examined. NOEL = 2000 mg/kg (highest dose tested). Study is acceptable, with no adverse effects. Aldous, 11/30/12.

## 90-day neurotoxicity, rat **

**53174-0038 264897 Buesen, R., S. Groeters, M. Becker, and B. van Ravenzwaay, "BAS 9210 I (cyflumetofen) - repeated dose 90-day oral neurotoxicity study in Wistar rats - administration via the diet," BASF SE, Ludwigshafen, Germany, Nov. 4, 2011. BASF # 2011/1178313. Groups of 10 Wistar rats/sex/group were dosed in diet with 0, 500, 1500, or 5000 ppm BAS 9210 I (cyflumetofen), purity 97.08%, Lot No. 01H1 for 13 weeks. Respective treated males received 30, 89, and 293 mg/kg/day, whereas females received 41, 99, and 353 mg/kg/day, respectively. Functional observational battery (FOB) and motor activity tests were conducted on days -7, 1, 22, 50, and 85. Neurohistopathology was assessed on 5 rats/sex/group in with controls and high dose rats. As there were no effects at the highest dose, intermediate groups were not examined. NOEL = 500 ppm, based on vacuolation in the adrenal cortex and increased adrenal weights in both sexes at 1500 to 5000 ppm. There were no findings of nervous

system tissue pathology nor of behavioral alterations. Study is acceptable, with no adverse effects. Aldous, July 5, 2012.

## IMMUNOTOXICITY**

** 53174-0058; 264931; "BAS 9210 I (Cyflumetofen) - Immunotoxicity Study in Female Wistar Rats-Administration via the Diet for 4 Weeks"; ®. Buesen, V. Strauss, C.R. Moreno, E. Fabian, B. van Ravenzwaay; Experimental Toxicology and Ecology, BASF SE, 67056 Ludwigshafen, Germany; Project No. 42C0510/09S015; 1/20/11); Eight Crl:WI (Han) female rats/group received 0, 500, 1500, or 5000 ppm of BAS 9210 I (Cyflumetofen technical) (batch no.; 01H1; purity: 97.08%) in the diet for 4 weeks (0, 33.2, 106.6, 349 mg/kg/day). On study day 23, the study animals were injected ip with 0.5 ml of $4x10^8$ sheep red blood cells (SRBC)/ml. On study day 29, prior to necropsy, blood was drawn from the retro-orbital sinus of each animal and humoral function was evaluated by analyzing the SRBC-specific IgM levels in the serum by means of an enzyme-linked immunosorbent assay (ELISA). No deaths resulted from the treatment. There was no treatment-related effect upon the mean body weights or food consumption. No treatment-related clinical signs were evident. There was no treatment-related effect upon the mean absolute or relative thymus or spleen weights. The absolute and relative adrenal gland weights were greater for the 500 ppm treatment group and above ($p<0.05$ or 0.01). In the histopathological examination, cytoplasmic vacuolation was noted in the adrenal cortex of all of the animals in the 1500 and 5000 ppm treatment groups. The treatment did not suppress the primary humoral response to SRBC. **No adverse effect indicated. Rat 28-Day Immunotoxicity NOEL:** (F) 5000 ppm, (349 mg/kg/day) (based upon the lack of treatment-related effects at the highest treatment level on the immunologically-related organs)**; Study acceptable.** (Moore, 6/21/12)

## ENDOCRINE DISRUPTOR STUDIES†

53174-0081 266522 Foster, J. R., "Cyflumetofen - aromatase (human recombinant) assay," Huntingdon Life Sciences, Ltd., Alconbury, Cambridgeshire, England, Nov. 11, 2011. BASF # OTSA-0577-FR. Human CYP19 + P450 reductase Supersomes™ (Gentest, BD Biosciences) were deployed in the presence of necessary cofactors and aromatase. Aromatase activity was assayed using [1-β-$^3$H]androstenedione as substrate, which releases tritiated water into the medium when transformed by aromatase into estrone. Removal of unreacted androstenedione by methylene chloride extraction after the 15-min incubation allowed tritium in aqueous phase to be assayed by scintillation counting as a measure of aromatase activity. Cyflumetofen [99.5% purity, Lot No. 009020] concentrations were 0.1, 1, 10, 100, 1000, 3160, 10000, and 31600 nM (limited by solubility). Positive control, formestane, ranged from 0.1 to 10000 nM. The lowest activity level of cyflumetofen at any concentration was 91% of concurrent control, designated as a negative response. Slightly over 32 nM with the positive control achieved 50% aromatase inhibition. Valid supplementary data. Aldous, Sept. 5, 2012.

53174-0081 266523 Akhurst, L. C., "Cyflumetofen - Estrogen receptor transcriptional activation (Human cell line (HeLa-9903))," Huntingdon Life Sciences, Ltd., Alconbury, Cambridgeshire, England, Dec. 14, 2011. BASF # OTSA-0578-FR. Test cells have two inserted constructs: hERα and firefly luciferase. When ligands bind to hERα, released luciferase can be

assayed to determine extent of binding. Responses were reported in terms of responses relative to the maximum positive control response (i.e. to the $RPC_{max}$ for 17 β-estradiol). The $RPC_{max}$ for cyflumetofen at the highest level tested ($10^{-5}$ M, i.e. 10 µM, based on solubility limitations) for the three tests were 7.8%, 10.4%, and 4.3%. This is a negative response in accordance with study criteria. By comparison, 17 β-estradiol gave about 50% of maximal response at about $10^{-11}$ M, compared to the weaker estrogenic effect of 17α-estradiol (50% response at about $10^{-9}$ M), and to the very weak response of 17α-methyltestosterone (50% response at about $10^{-6}$ M). Corticosterone did not elicit any consistent response at its highest dose of $10^{-4}$ M, nor at lower concentrations. Valid supplementary data. Aldous, Sept. 10, 2012.

**53174-0081 266524** Akhurst, L. C., "Cyflumetofen - H295R Steroidogenesis Assay," Huntingdon Life Sciences, Ltd., Alconbury, Cambridgeshire, England, 12/20/11. BASF # OTSA-0579-FR. H295R human adrenocortical carcinoma cell line (ATCC CRL-2128) test cells release testosterone and estradiol into supernatant. These hormones in supernatants were assayed by ELISA methods. Concentrations of these hormones in supernatants of cultured cells in presence of cyflumetofen (99.5% purity, Lot No. 009020) were compared to basal levels, and to alterations caused by a known inducer (forskolin) and a known inhibitor (prochloraz). Cells were seeded into 24-well plates, and were at about 60% confluency for treatment initiation. Exposure duration was 48 hours at 37 °C. Generally cyflumetofen was evaluated at 10 µM, 5 µM, 1 µM, and at subsequent 10x dilutions to 100 pM. Cytotoxicity threshold for a viable reading was exceeded in one of 3 tests at 10 µM cyflumetofen. Forskolin reliably increased estradiol and testosterone concentrations (about 7x to 10x, and about 1.6x, respectively) at 1 µM. Prochloraz, reliably decreased concentrations of both hormones in the range of 0.1 to 1 µM. Cyflumetofen at 10 µM increased estradiol about 2x over solvent control, and decreased testosterone to about 0.5x of control. Significant changes in the same directions were observed at 5 µM for both hormones. A slight but significant decrease in testosterone was observed in 2 of the 3 tests at 1 µM. Thus cyflumetofen alters cellular release of testosterone and of estradiol in this system at and slightly below cytotoxic cyflumetofen concentrations. Valid supplementary study. Aldous, Sept. 10, 2012.

53174-0081 266525 Matthews, A., "Cyflumetofen - Oestrogen receptor binding assay using rat uterine cytosol," Huntingdon Life Sciences, Ltd., Alconbury, Cambridgeshire, England, Jan. 10, 2012. BASF # OTSA-0581-FR. In the competitive binding assays, cyflumetofen [Cyflumetofen, 99.5% purity, Lot No. 009020] concentrations were 0.1, 1, 10, 100, 1000, 10000, 31600, or 100000 nM. Highest dose was based on precipitate at 316000 nM. There were three tests, with each level in triplicate. Under study conditions, there was an acceptable 12% of radioligand [$^{3}$H-estradiol] binding at 0.3 mg protein/ml, with acceptable non-specific binding (< 15%). Positive response was defined for this study as > 50% displacement of radioactive estradiol from the receptor. Under study conditions, [cold] estradiol caused about 50% of label displacement at 1 nM. Displacement with 19-norethindrone [a weaker binding ligand] was about 50% at 1 mM. Octyltriethoxysilane (negative control) did not show any receptor activity, nor did cyflumetofen. Thus cyflumetofen was determined to be "not interactive" with the estrogen receptor. Valid supplementary data. Aldous, 9/14/12.

53174-0081 266526 Willoughby, J. A., "Cyflumetofen: androgen receptor binding - (rat prostate cytosol)," CeeTox, Inc., Kalamazoo, MI, Jan. 9, 2012. BASF # OTSA-0594-FR.

Cyflumetofen, 99.5% purity, Lot No. 009020, was initially evaluated at $10^{-3}$ M, and 10-x dilutions to $10^{-11}$ M. The next two assays used concentrations from $10^{-4}$ M to $10^{-11}$ M. In the first assay, precipitation was observed at $10^{-3}$ M and $10^{-4}$ M, so that those results were not assessed. There was no precipitation evident at $10^{-4}$ M in the second and third trials, so that result was usable. Reference androgen binding ligand, [$^{3}$H]-R1881, was tested at $10^{-6}$ M to $10^{-11}$ M, and the weak-affinity ligand, dexamethasone, was tested at 10-x intervals from $10^{-3}$ M to $10^{-10}$ M. [$^{3}$H]-R1881 had 50% binding at about $10^{-9}$ M. The weak-affinity ligand, dexamethasone, achieved 50% binding between $10^{-4}$ M and $10^{-5}$ M. Cyflumetofen specific binding ranged from 84% to 102% at all concentrations tested in the three independent tests. Thus cyflumetofen is considered as a "non-binder" under guidelines of the assay. Valid screening assay. Aldous, 9/19/12.

## OTHER MECHANISTIC STUDY

53174-0060 264938 Takeda, M., "OK-5101 Technical: mechanistic study on the mode of toxic effects in rats," The Institute of Environmental Toxicology, Ibaraki, Japan, June 8, 2006. BASF # OTSA-0278(EN)-FR. Groups of 8 to 10 Fisher rats/sex/group were dosed in diet with 0, 100, or 5000 ppm OK-5101 (Cyflumetofen), purity 97.67%, Lot No. 01D1 for 4 weeks in a supplementary study. Achieved dose levels were 7.4 and 378 mg/kg/day for treated males, and 7.6 and 347 mg/kg/day for females. Major parameters included serum hormonal assays (ACTH and corticosterone) and quantitative analysis of adrenal gene expression [CYP11A1, CYP11B1, neutral cholesteryl ester hydrolase (NCEH), and hormone-sensitive lipase (HSL)]. Adrenal gland cholesterol content was assayed (free, esterified, and total cholesterol). Adrenals and ovaries were weighed, examined grossly, and subjected to microscopic evaluation. Limited SEM evaluations were done to assess vacuolation effects. There were no effects at 100 ppm: all findings here refer to 5000 ppm. There were no premature deaths nor clinical signs. Body weights and food consumption were unaffected. Hormone levels of ACTH and corticosterone were unaffected. Adrenals in both sexes were grossly enlarged at necropsy, with adrenal weights significantly elevated. There were no treatment-related changes in ovaries. Histopathology confirmed vacuolation of the adrenal cortical zona glomerulosa and zona fasciculata, and vacuolation of ovarian interstitial cells. Droplet sizes in male adrenals tended to be larger than those for females. Gene expression evaluations from adrenal gland indicated modest increases in CYP11A1 in both sexes (significant in females), a modest decrease in CYP11B1 in females, and particularly a decrease in HSL (significant in females). Cholesterol forms in the adrenal gland (total, ester, and free) were elevated in all categories in both sexes, often significantly. This appears to relate to the vacuolation noted. Increased content of adrenal gland cholesterol (total, ester, and free cholesterol in both sexes) appears to reflect this vacuolation. The investigator proposed that an inhibition of HSL, a rate-limiting step in processing of cholesterol esters, was the key mechanism of action. Possibly an inhibition of HSL by cyflumetofen caused a sequestration of cholesterol (particularly esterified) in adrenal cortical cells, which would account for the observed increased vacuolation. It is not clear if the degree of HSL inhibition demonstrated was sufficient to elicit the build-up of cholesterol products and the vacuolation seen in this study. Useful supplementary data. Aldous, June 12, 2012.

## STUDIES ON METABOLITES AND IMPURITIES†

53174-0082 266527 Verspeek-Rip, C. M., "Evaluation of the mutagenic activity of AB13 (impurity of OK-5101) in an *in vitro* mammalian cell gene mutation test with L5178Y mouse lymphoma cells (with independent repeat)," Notox B. V., 's-Hertogenbosch, The Netherlands, 7/14/04. BASF # OTSA-0194. [Forward mutation study with L5178Y/TK$^{+/-}$ phenotype, and trifluorothymidine for selection]. AB13, an impurity of cyflumetofen, Batch HN0305021, 99.2% purity, was evaluated at 0.03, 0.1, 0.3, 1, 3, 10, 33, and 100 µg/ml in two trials with and without S-9. There was precipitate at 100 µg/ml, and no cytotoxicity at any dose. Both trials with activation involved 3 hr exposure, whereas without S-9 the trials evaluated 3 hrs and 24 hrs, respectively. Positive controls were MMS without S-9 at 15 µg/ml (3-hr exposure) or 5 µg/ml (24-hr treatment) and cyclophosphamide with S-9 at 10 µg/ml. There were no responses to test article (including colony size), whereas positive controls elevated mutant frequency roughly 10-fold over controls and AB13 groups. Valid supplementary study, with no adverse effects. Aldous, 9/20/12.

53174-0061; 264945; "Evaluation of the Mutagenic Activity of B-1 in the *Salmonella typhimurium* Reverse Mutation Assay and the *Escherichia coli* Reverse Mutation Assay (with Independent Repeat); (C.M. Verspeek-Rip; Notox B.V., 5231 DD's - Hertogenbosch, The Netherlands; Project No. 396113; 6/15/04); *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and *E. coli* strain WP2 *uvr*A were treated for 48 hours at 37$^{o}$ C with B-1 (Cyflumetofen plant metabolite) (batch no. FHE01; purity: 99.0%) at concentrations ranging from 100 to 5000 µg/plate ((+/-) activation in two trials. Each treatment level was plated in triplicate. An S9 fraction derived from the livers of rats pre-treated with Aroclor 1254 was used to metabolize the test material. There was no increase in the incidence of reverse mutation for any of the strains under conditions of (+/-) activation in either trial. **No adverse effect indicated.** Positive controls were functional. **Study acceptable.** (Moore, 7/10/12)

53174-0061; 264946; "Evaluation of the Ability of B-1 to Induce Chromosomal Aberrations in Cultured Peripheral Human Lymphocytes"; (C.A.F. Buskens; Notox B.V., 5231 DD's - Hertogenbosch, The Netherlands; Project No. 396146; 6/21/04); Primary human lymphocyte cultures, procured from the whole blood of male volunteers (stimulated with PHA for 48 hours), were treated with concentrations of B-1 (Cyflumetofen plant metabolite) (batch no. FHE01; purity: 99.0%) ranging from 333 to 1901 µg/ml for 3 hours, followed by a recovery period of 20 to 22 hours of incubation under conditions of both non-activation and activation in Trial No. 1. In Trial No. 2, the cells were treated with concentrations of the test material ranging from 100 to 1000 µg/ml for 24 hours or from 100 to 1901 µg/ml for 48 hours (non-activation) or from 333 to 1901 µg/ml for 3 hours, followed by a recovery period of 44 to 46 hours prior to being harvested (activation). An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. No treatment-related increase in chromosomal aberrations was evident under conditions of either non-activation or activation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 7/11/12)

**** 53174-0061; 264947**; "Evaluation of the Mutagenic Activity of B-1 in an *In Vitro* Mammalian Cell Gene Mutation Test with L5178Y Mouse Lymphoma Cells (with Independent Repeat)"; (C.M. Verspeek-Rip; Notox B.V., 5231 DD's - Hertogenbosch, The Netherlands; Project ID No. 396179; 12/22/04); Mouse lymphoma L5178Y cells (clone 3.7.2C (TK$^{+/-}$)) were

treated with B-1 (Cyflumetofen plant metabolite) (batch no. FHE01; purity: 99.0%) at concentrations ranging from 1 to 1901 µg/ml (+/- activation) for 3 hours at 37$^{o}$ C. in the first trial. In the 2$^{nd}$ trial, the cells were exposed to concentrations ranging from 1 to 1901 µg/ml for 24 hours under conditions of non-activation and from 3 to 1901 µg/ml for 3 hours under conditions of activation. In the 3$^{rd}$ trial, the cells were exposed to concentrations ranging from 3 to 1901 µg/ml for 24 hours under conditions of non-activation. The vehicle control samples were incubated in duplicate. Single cultures were performed for each treatment level. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. The size of the mutant colonies was reported as a bimodal distribution. There was treatment-related increase in the mutation frequency for the non-activated samples at treatment levels of 1500 µg/ml and above. The positive controls were functional. **Possible adverse effect indicated. Study acceptable.** (Moore, 7/12/12)

** 53174-0061; 264948; "Evaluation of DNA Repair Inducing Ability of B-1 in Male Rat Hepatocytes (*In Vivo* Rat Hepatocyte DNA-Repair Assay); (C.A.F. Buskens; Notox B.V., 5231 DD's - Hertogenbosch, The Netherlands; Project ID No. 490348; 4/23/09); Six male Wistar rats/group were dosed orally by gavage with 1000 or 2000 mg/kg of B-1 (Cyflumetofen plant metabolite) (batch no. YaEu806019; purity: 99.1%). Two animals were dosed with the vehicle, corn oil, and one animal each was dosed with dimethylnitrosamine (DMN), 10 mg/kg, or 2-acetylaminofluorene (2-AAF), 50 mg/kg, as positive controls. Three animals/group in the treatment groups and 1 animal in the vehicle control group and the DMN positive control animal were euthanized at 2-4 hours post-dose. The 3 remaining animals/group in the treatment groups, the remaining vehicle control animal and the 2-AAF positive control animal were euthanized at 12-16 hours post-dose. Hepatocytes were isolated and viability was determined by trypan blue dye exclusion. After attachment, cells were exposed to (methyl-$^{3}$H) thymidine for 4 hours followed by an overnight incubation with unlabeled thymidine. One hundred cells were scored per animal. No increase in the net nuclear grain counts was evident at any dose level or sampling time. **No adverse effect indicated**. The positive control was functional. **Study Acceptable**. (Moore, 7/13/12).

**** 53174-0062; 264950**; "Evaluation of the Mutagenic Activity of 2-(Trifluoromethyl) benzamide, B-3 in the *Salmonella typhimurium* Reverse Mutation Assay and the *Escherichia coli* Reverse Mutation Assay (with Independent Repeat)"; (C.M. Verspeek-Rip; Notox B.V., 5231 DD's - Hertogenbosch, The Netherlands; Project ID. No. 489612; 4/23/09); *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and *E. coli* strain WP2 *uvr*A were treated for 48 hours at 37$^{o}$ C with 2-(Trifluoromethyl)benzamide (B-3) (Cyflumetofen soil metabolite) (batch no. MA08015; purity: 99.1%) at concentrations ranging from 100 to 5000 µg/plate +/- activation in two trials. Each treatment level was plated in triplicate. An S9 fraction derived from the livers of rats pre-treated with phenobarbital/B-naphthoflavone was used to metabolize the test material. There was an increase in the incidence of reverse mutation for the strain TA100 under conditions of non-activation. **Possible adverse effect indicated.** Positive controls were functional. **Study acceptable.** (Moore, 7/16/12)

** 53174-0062; 264951; "Evaluation of the Ability of 2-(Trifluoromethyl)benzamide, B-3 to Induce Chromosomal Aberrations in Cultured Peripheral Human Lymphocytes (with Repeat Experiment); (C.A.F. Buskens; Notox B.V., 5231 DD's - Hertogenbosch, The Netherlands;

Project No. ID. 489613; 4/16/09); Primary human lymphocyte cultures, procured from the whole blood of male volunteers (stimulated with PHA for 48 hours), were treated with concentrations of 2-(Trifluoromethyl)benzamide (B-3) (Cyflumetofen soil metabolite); batch no. MA080115; purity: 99.1%) ranging from 333 to 1891 µg/ml for 3 hours, followed by a recovery period of 21 hours of incubation under conditions of both non-activation and activation in Trial No. 1. In Trial No. 2, the cells were treated with concentrations of the test material ranging from 100 to 1891 µg/ml for 24 hours, from 33 to 1891 µg/ml for 48 hours (non-activation) or from 333 to 1891 µg/ml for 3 hours, followed by a recovery period of 45 hours prior to being harvested (activation). An S9 fraction derived from the livers of rats pre-treated with phenobarbital/B-naphthoflavone was used to metabolize the test material. No treatment-related increase in chromosomal aberrations was evident under conditions of either non-activation or activation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 7/16/12)

**** 53174-0062; 264952**; "Evaluation of the Mutagenic Activity of 2-(Trifluoromethyl) benzamide, B-3 in an *In Vitro* Mammalian Cell Gene Mutation Test with L5178Y Mouse Lymphoma Cells (with Independent Repeat)"; (C.M. Verspeek-Rip; Notox B.V., 5231 DD's - Hertogenbosch, The Netherlands; Project ID No. 486614; 4/20/09); Mouse lymphoma L5178Y cells (clone 3.7.2C ($TK^{+/-}$)) were treated with 2-(Trifluoromethyl)benzamide (B-3) (Cyflumetofen soil metabolite) (batch no. MA080115; purity: 99.1%) at concentrations ranging from 1 to 1891 µg/ml (+/- activation) for 3 hours at $37^{o}$ C. in the first trial. In the 2nd trial, the cells were exposed to concentrations ranging from 1 to 1891 µg/ml for 24 hours under conditions of non-activation and from 1 to 1891 µg/ml for 3 hours under conditions of activation. The vehicle control samples were incubated in duplicate. Single cultures were performed for each treatment level. An S9 fraction derived from the livers of rats pre-treated with phenobarbital/B-naphthoflavone was used to metabolize the test material. The size of the mutant colonies was reported as a bimodal distribution. There was treatment-related increase in the mutation frequency for the non-activated samples. The positive controls were functional. **Possible adverse effect indicated. Study acceptable.** (Moore, 7/17/12)

** 53174-0062; 264953; "Evaluation of DNA Repair Inducing Ability of 2-(Trifluoromethyl)benzamide, B-3 in Male Rat Hepatocytes (*In Vivo* Rat Hepatocyte DNA-Repair Assay); (C.A.F. Buskens; Notox B.V., 5231 DD's - Hertogenbosch, The Netherlands; Project ID No. 490347; 4/23/09); Six male Wistar rats/group were dosed orally by gavage with 175 or 350 mg/kg of 2-(Trifluoromethyl)benzamide (B-3) (Cyflumetofen soil metabolite) (Batch no. MA080115; purity: 99.1%). Two animals were dosed with the vehicle, corn oil, and one animal each was dosed with dimethylnitrosome (DMN), 10 mg/kg, or 2-acetylaminofluorene (2-AAF), 50 mg/kg, as positive controls. Three animals/group in the treatment groups and 1 animal in the vehicle control group and the DMN positive control animal were euthanized at 2-4 hours post-dose. The 3 remaining animals/group in the treatment groups, the remaining vehicle control animal and the 2-AAF positive control animal were euthanized at 12-16 hours post-dose. Hepatocytes were isolated and viability was determined by trypan blue dye exclusion. After attachment, cells were exposed to (methyl-$^{3}H$) thymidine for 4 hours followed by an overnight incubation with unlabeled thymidine. One hundred cells were scored per animal. No increase in the net nuclear grain counts was evident at any dose level or sampling time. **No adverse effect indicated**. The positive control was functional. **Study Acceptable**. (Moore, 7/18/12).

** 53174-0063; 264956; "Evaluation of the Mutagenic Activity of AB-13 (Impurity of OK-5101) in the *Salmonella typhimurium* Reverse Mutation Assay and the *Escherichia coli* Reverse Mutation Assay (with Independent Repeat)"; (C.A.F. Buskens; Notox B.V., 5231 DD's - Hertogenbosch, The Netherlands; Project ID No. 407846; 8/19/04); *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and *E. coli* strain WP2 *uvr*A were treated for 48 hours at 37$^{o}$ C with AB-13 (Cyflumetofen plant metabolite) (batch no. FHE01; purity: 99.0%) at concentrations ranging from 3 to 333 µg/plate ((+/-) activation in two trials. Each treatment level was plated in triplicate. An S9 fraction derived from the livers of rats pre-treated with Aroclor 1254 was used to metabolize the test material. There was no increase in the incidence of reverse mutation for any of the strains under conditions of (+/-) activation in either trial. **No adverse effect indicated.** Positive controls were functional. **Study acceptable.** (Moore, 7/13/12)

** 53174-0063; 264957; "Evaluation of the Ability of AB-13 (Impurity of OK-5101) to Induce Chromosomal Aberrations in Cultured Peripheral Human Lymphocytes (with Repeat Experiment)"; (C.A.F. Buskens; Notox B.V., 5231 DD's - Hertogenbosch, The Netherlands; Project ID No. 407857; 7/13/04); Primary human lymphocyte cultures, procured from the whole blood of male volunteers (stimulated with PHA for 48 hours), were treated with concentrations of AB-13 (Cyflumetofen Manufacturing Impurity) (batch no. HN0305021; purity: 99.2%) ranging from 33 to 333 µg/ml for 3 hours, followed by a recovery period of 21 hours of incubation under conditions of both non-activation and activation in Trial No. 1. In Trial No. 2, the cells were treated with concentrations of the test material ranging from 10 to 333 µg/ml for 24 and 48 hours (non-activation) or for 3 hours (activation), followed by a recovery period of 45 hours prior to being harvested (activation). An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. No treatment-related increase in chromosomal aberrations was evident under conditions of either non-activation or activation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 7/16/12)

**Overall assessment of positive findings of cyflumetofen metabolites or impurities in mutagenicity studies:**

Record No. 264947 reported positive response metabolite "B1" in the *in Vitro* Mammalian Cell Gene Mutation Test with L5178Y Mouse Lymphoma Cells. This test article is described in the 1-liner as a "plant metabolite," however it is also an abundant metabolite in rat urine and feces (constituting at least 25% of administered dose following low dose administration to males and females: Record 264923, p. 21). B1 is 2-(trifluoromethyl)benzoic acid, which would be expected to be easily excreted from the body. About 2-fold increase in mutation frequency was observed with and without S-9 in the first test with 3-hr exposure at 1000 to 1901 µg/ml. In the second test, 1901 µg/ml B1 (without S-9, with 24-hr incubation) increased mutation frequency (8.2-fold), with only 9% relative total growth (RTG) at that dose. In that test, the next lower dose of 1000 µg/ml B1 did not affect mutant frequency, with 34% RTG. A third test (without S-9, with 24-hr incubation) elicited 2.5x and 7.0x increases in mutation frequency at 1500 and 1901 µg/ml, respectively, with no effect at 1000 µg/ml. This sharp dose-response of a mobile metabolite tested *in vitro* does not represent a major concern.

There were two records showing positive mutagenic responses of metabolite "B-3," 2-(trifluoromethyl)benzamide, a cyflumetofen soil metabolite. In Record No. 264952, a L5178Y mouse lymphoma assay as above, the primary finding of interest was an increase in mutant frequency without S-9, after 24-hr incubation, in the range of 1000 to 1891 µg/ml, with mutant frequencies of about 2x and 4x, respectively. Relative total growth was inhibited at 1891 µg/ml only (to 53% of controls). In a bacterial reverse mutation assay (Record No. 264950), only strain TA100 showed responses. In general, 1000 µg/ml with or without S-9 caused no response, whereas 3330 to 5000 µg/ml (with or without S-9) elicited a maximum of about 2x increase. B-3 was not a common metabolite in rat studies (Record 264923, p. 21). These findings do not warrant a major concern.

## ACUTE TESTS ON CYFLUMETOFEN METABOLITES OR IMPURITIES

53174-0061; 264944; "Assessment of Acute Oral Toxicity with B-1 in the Rat (Acute Toxic Class Method)"; C. G. M. Beerens-Heijnen; Notox B.V., 5231 DD's - Hertogenbosch, The Netherlands; Project No. 396089; 11/1/04); Six female Wistar rats were dosed orally by gavage with 2000 mg/kg of B-1 (Cyflumetofen plant metabolite) (batch no. FHE01; purity: 99.0%). No deaths resulted from the treatment. Hunched posture, lethargy, uncoordinated movements and/or piloerection were noted between study days 1 and 3. No treatment-related lesions were evident in the necropsy examination. LD50 (F) > 2000 mg/kg; Toxicity Category III; **Study acceptable.** (Moore, 7/9/12)

53174-0063; 264955; "Assessment of Acute Oral Toxicity with AB-13 (Analytical Grade) in the Rat (Acute Toxic Class Method)"; (M.S. Teunissen; Notox B.V., 5231 DD's - Hertogenbosch, The Netherlands; Project ID No. 407835; 8/9/04); Six female Wistar rats were dosed orally by gavage with 2000 mg/kg of AB-13 (Cyflumetofen plant metabolite) (batch no. FHE01; purity: 99.0%). No deaths resulted from the treatment. Hunched posture, shallow respiration, and uncoordinated movements were noted between study days 1 and 2. No treatment-related lesions were evident in the necropsy examination. LD50 (F) > 2000 mg/kg; Toxicity Category III; **Study acceptable.** (Moore, 7/13/12)

## SUMMARIES OF CLASSES OF STUDIES: NO INDIVIDUAL STUDIES TO REVIEW

53174-0032 264877 "Toxicology summary for Cyflumetofen (BAS 9210 I)," BASF, 11/21/11.

53174-0033 264878 "Multi-lateral submission for the evaluation of the active substance BAS 9210 I - Cyflumetofen," (summary and evaluation of toxicological and metabolism studies for OECD)

## SUPPLEMENTAL STUDIES†

53174-0060 264942 Inui, T., "Pharmacology study of OK-5101 - effects on the respiratory / cardiovascular system in dogs," Panapharm Laboratories Co., Kumamoto, Japan, 9/16/03 (as

amended). BASF # 2003/1032459. Four beagles were dosed once by gelatin capsule with 2000 mg/kg of OK-5101, Lot 01D1, purity 97.67 % in a study to evaluated blood pressure, heart rate, breathing rate, and major EKG interval durations. Each dog received cyflumetofen either one week before or one week after receiving a blank capsule, and the above measurements following cyflumetofen treatment were compared to empty capsule treatments. None of the evaluated criteria elicited changes in these parameters. Useful supplementary data. Aldous, Nov. 9, 2012.

53174-0087, 266937 "BAS 921021 – Bovine Corneal Opacity and Permeability Test (BCOP Test)", supplemental, Remmele, M., Experimental Toxicology and Ecology, BASF SE, Germany. 10/18/2011. Study identification no. 63V0348/11A270. BAS 921021, Batch No. 1742-56, a liquid containing 19.0% w/w active ingredients. A single topical dose of 750 µl of the undiluted test substance, highly de-ionized water (negative control, NC), or 0.4% (w/v) NaOH solution (Positive control, PC), was applied to the epithelial surface of isolated bovine corneas, in triplicates, for 10 minutes, followed by a 2-hours post-incubation period. Corneal opacity and permeability was measured and an *In Vitro* Irritancy score was calculated of the test substance relative to the control corneas. H&E-stained cross sections of the treated corneas were evaluated for the irritation potential of the test substance. The test showed the test substance had an *In Vitro* Irritancy score of 1.6, compared with 0.7 for negative control material and 61.5 for positive control material. There were no histological findings indicating eye irritation at histological evaluation. **The test substance did not cause serious eye damage in the test. Supplemental.** (Pan & Leung, 10/19/12)

53174-0087, 266938 "BAS 921021 – EpiOcular™ eye irritation test", supplemental, Remmele, M., Experimental Toxicology and Ecology, BASF SE, Germany. 10/18/2011. Study identification no. 62V0348/11A269. BAS 921021, Batch No. 1742-56, a liquid containing 19.0% w/w active ingredients. The eye irritation potential of the test substance was examined by using the three dimensional human cornea model EpiOcular™. Fifty microliters of test substance (undiluted), highly de-ionized water (Negative control, NC) or 98+% methyl acetate (Positive control, PC) was applied to two tissues of EpiOcular™ for 30 minutes in incubator at 37°C, followed by rinsing in PBS and post-incubation in a standard culture condition for 2 hours. The tissues were then allowed to be incubated with 0.3 ml of MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazodium bromide, 1.0 mg/ml) for 3 hours in the incubator, washed, and the metabolic product formazan was extracted by incubation of the tissues in isopropanol at room temperature overnight or for at least 2 hours on a plate shaker. The optical density at a wavelength of 570 nm ($OD_{570}$) of the extracts was determined spectrophotometrically. The tissue viability, the quotient of the $OD_{570}$ of tissues treated with the test material and the mean $OD_{570}$ value of the NC is used to evaluate whether or not a test material is an irritant. The test material produced a viability of 95%, while the NC produced 100% and the PC produced 15%. Therefore, the test material did not show an eye irritation potential in the EpiOcular™ eye irritation test under the test conditions chosen. **Supplemental.** (Pan & Leung, 10/19/12)

0102, 274703; "BAS 9210 I (Cyflumetofen): Carcinogenicity Study in Mice" (Yoshida, T., The Institute of Environmental Toxicology, Ibaraki, Japan, Study Identification Number(s) IET 11-0016, BASF Project No.: 87C0510/09X065, 08/08/2013). 870.4200. BAS 9210 I (Cyflumetofen) (BASF test substance number: 09/0510-3 (009025), purity = 97.82%) was admixed to the diet and fed to 52 (SPF) ICR mice [Crlj:CD1(ICR)] per sex per dose at dose

levels of 0 (basal diet only) or 10000 ppm (0 and 1143 mg/kg/day, respectively for males and 0 and 1132 mg/kg/day, respectively for females) continuously for more than 78 weeks. Mortality at week 78- males: 20/52, 17/52, respectively; females: 3/52, 17/52, respectively (increased mortality rates for the females were not treatment-related because they were within the historical control range). No treatment-related clinical signs were observed in males. Treatment-related increased incidences of pale-colored skin and pale-colored eye/eyelid were observed in females. No treatment-related effects on body weight or food consumption were observed. A treatment-related increase in mean relative adrenal weight was observed in females. Macroscopic examination revealed treatment-related enlarged spleens in females. Microscopic examination revealed treatment-related increased extramedullary hematopoiesis in the spleen in females, deposition of brown pigment at the cortico-medullary region of the adrenals in both sexes, and vacuolation in the cortical cells of the adrenals in both sexes. **No adverse effects indicated.** NOEL (M) < 1143 mg/kg/day (10000 ppm) and NOEL (F) < 1132 mg/kg/day (10000 ppm) based on an increase in mean relative adrenal weight (females), enlarged spleen (females), increased extramedullary hematopoiesis in the spleen (females), deposition of brown pigment at the cortico-medullary region of the adrenals (both sexes), and vacuolation in the cortical cells of the adrenals (both sexes). No treatment-related neoplastic changes were observed. **Supplemental study** (only one dose level was used)**.** (Corlett and Leung, 02/13/2014)

**0103, 274706**; "BAS 9210 I (Cyflumetofen): Carcinogenicity Study in Rats" (Takahashi, N., The Institute of Environmental Toxicology, Ibaraki, Japan, Laboratory Project ID IET 11-0002, BASF Project No.: 82C0510/09X066, 10/07/2013). 870.4200. BAS 9210 I (Cyflumetofen) (BASF test substance number: 09/0510-3 (009025), purity = 97.82%) was admixed to the diet and fed to 50 (SPF) Fischer rats [F344/DuCrlCrlj] per sex per dose at dose levels of 0 (basal diet only) or 6000 ppm (0 and 220 mg/kg/day, respectively for males and 0 and 287 mg/kg/day, respectively for females) continuously for more than 104 weeks. No treatment-related mortality occurred. No treatment-related clinical signs were observed in males; treatment-related incidences of tactile hair loss and soiled fur were observed in females. A treatment-related decrease in body weight compared to the control group animals was observed in both sexes. No treatment-related effect on food consumption was observed. Hematology revealed no findings of toxicologic significance. Treatment-related increases in mean relative liver, kidney, and adrenal gland weights in both sexes were observed. Macroscopic examination revealed a treatment-related increase in testicular masses. Microscopic examination revealed a treatment-related increase in atrophy in the acinar cells of the pancreas in males, a treatment-related increase in diffuse hypertrophy of the cortical cells in the adrenal glands in both sexes and a higher incidence of interstitial cell tumor in the testes. **Possible adverse effect indicated:** higher incidence of interstitial cell tumor in the testes. NOEL (M) < 220 mg/kg/day (6000 ppm) and NOEL (F) < 287 mg/kg/day (6000 ppm) based on decreased mean body weight, increased mean relative liver, kidney, and adrenal weights, and an increase in diffuse hypertrophy of the cortical cells in the adrenal glands in both sexes, and higher incidence of interstitial cell tumor in the testes. **Supplemental study** (only one dose level was used)**.** (Corlett and Leung, 03/05/2014)

0101, 270815; "BAS 9210 I (Cyflumetofen): Repeated Dose 1-Year Oral Toxicity Study in Rats" (Yoshida, T., The Institute of Environmental Toxicology (IET), Ibaraki, Japan, Study Identification Number(s) IET 11-0001, BASF Project No.:70C0510/09X067, 11/21/2012). BAS 9210 I (Cyflumetofen), technical grade (BASF test substance number 09/0510-3 (009025), purity

= 97.82%) was admixed to the diet and fed to 20 (SPF) Fischer rats (F344/DuCrlCrlj) per sex per dose at dose levels of 0 (basal diet only) or 6000 ppm (0 and 250 mg/kg/day, respectively for males and 0 and 319 mg/kg/day, respectively for females) continuously for 52 weeks. The study also included a satellite group of animals consisting of 30 rats per sex per dose (dose levels of 0 and 6000 ppm) that were subjected to interim examinations and sacrificed (10 animals per sex per dose) after 4, 13, and 26 weeks of treatment. No animals died during the treatment period. Treatment-related soiled fur in the genital region was observed in main group females. Weekly detailed clinical observations on the main group animals revealed no treatment-related abnormalities. A treatment-related decrease in body weight in main group females was observed. No treatment-related effects on food consumption were observed. Hematological investigations revealed treatment-related decreases in mean platelet count (in satellite males and females), mean reticulocyte count (In main group males and satellite females), and mean fibrinogen concentration (in satellite group males and females), a treatment-related increase in mean prothrombin time (in satellite and main group males and satellite females), and a treatment-related increase in mean activated partial thromboplastin time (in satellite and main group males). Blood biochemistry investigations revealed treatment-related decreases in mean total cholesterol (in satellite group males and females) and mean triglycerides (in satellite group males and females and in main group males), and treatment-related increases in mean blood urea nitrogen (in satellite group males and females and in main group males), in mean total protein (in main group males), in mean albumin (in satellite and main group males), and in mean inorganic phosphorus concentration (in satellite group male and females). Treatment-related decreases in mean relative liver, adrenal and kidney weights were observed in satellite and main group males and females. Macroscopic examination revealed treatment-related enlarged adrenals in satellite and main group females and adrenals white in color in satellite and main group males and females. Microscopic examination revealed treatment-related diffuse vacuolation of the cortical cells in the adrenals in satellite and main group males and in diffuse hypertrophy of the cortical cells in the adrenals in satellite and main group females. Also, microscopic examination revealed treatment-related focal atrophy of acinar cells in the pancreas and hyperplasia of interstitial cells in the testes in the main group males and treatment-related vacuolation of interstitial gland cells in the ovaries in the main group females. **No adverse effects.** NOEL (M) < 250 mg/kg/day (6000 ppm) based on vacuolation present in the adrenal gland cortical cells and NOEL (F) < 319 mg/kg/day (6000 ppm) based on hypertrophy of the adrenal gland cortical cells. **Supplemental study** (only one dose level was used)**.** (Corlett and Leung, 12/17/2013)