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OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

MEMORANDUM

Date: June 30, 2010

SUBJECT: Fluxapyroxad (BAS 700F) New Chemical Screen for Toxicology

PC Codes: 138009
Decision Nos.: 431203

Petition No.: 0F7709
Risk Assessment Type: NA
TXR No: NA
MRID Nos: NA

DP Barcodes: D377679
ID No.: 7969-GRE-Xemium Fungicide Technical
Regulatory Action: Tox Screen
Case No.: NA
CAS No.: 907204-313
40 CFR: NA

Ver.Apr.08

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6/30/2010

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Registration Division (7505P)

Read in RRC 7/7/2010 EV

Action Requested: New Chemical Screen of toxicology studies.

1. HED Response:

Toxicology studies were submitted for a New Chemical Screen for a new technical grade active ingredient (TGAI), fluxapyroxad (BAS 700F, PC Code 138009), three impurities (Reg. Nos. 5356469, 5410775, 5425764), and three metabolites (M700F01, M700F02, M700F048). This new TGAI is to be considered for food use, and so must satisfy the food use pattern requirements for Title 40, Part 158, subpart F, §158.500 (Toxicology data requirements). The studies for the TGAI have been screened and are acceptable to begin the risk assessment.

Toxicity studies for the TGAI (BAS 700 F)

A "six-pack" of acute toxicity studies for the TGAI is required. These studies were submitted, fulfilling this requirement: 870.1100 (Acute oral toxicity –rat, MRID 47923558), 870.1200 (Acute dermal toxicity, MRID 47923559); 870.1300 (Acute inhalation toxicity – rat, MRID 47923560); 870.2400 (Primary eye irritation – rabbit; MRID 47923562): 870.2500 (Primary dermal irritation, MRID 47923561); 870.2600 (Dermal sensitization, MRID 47923563). An 870.6200a Acute neurotoxicity – rat is also required and was submitted (MRID 47923605).

The following subchronic toxicity studies for the TGAI are required and were submitted: 870.3100 (90–day Oral – rodent, MRID 47923567 rat study and MRID 47923568 mouse study); 870.3150 (90–day Oral - non-rodent (dog), MRID 47923569); 870.6200 (90–day Neurotoxicity – rat, MRID 47923606); 870.4100 (Chronic oral – rodent, MRID 47923591); 870.4200 (Oncogenicity-MRID 47923591 for rat and MRID 47923592 for mouse); 870.3700 prenatal development (MRID 47923603 for rat and MRID 47923604 for rabbit); 870.3800 (Reproduction and fertility effects-MRID 47923602); a mutagenicity battery (870.5100, Bacterial reverse mutation, MRID 47923572 and MRID 47923573, 870.5300, In vitro mammalian cell gene mutation test, MRID 47923580, In vitro mammalian mutation, MRID 27923577, 870.5375, In vitro chromosomal aberration, MRID 27923577, 870.5395 in vivo micronucleus, MRID 47923584); 870.7485 (Metabolism and pharmacokinetics, MRID 47923555, 47923556, and 47923557); 870.7800 (Immunotoxicity, MRID 47923633).

An 870.7600 dermal penetration study is conditionally required and was submitted (MRID 4793622).

The following are conditionally required for the TGAI and were not submitted: 870.3250 (90-day Dermal), 870.3465 (90-day Inhalation-rat), 870.6100 (28-day Delayed neurotoxicity-hen), 870.6300 (developmental neurotoxicity). *It is not anticipated that these studies will be required at this time to complete a human health risk assessment for this chemical, but the inhalation study is considered a data deficiency.*

Other studies submitted for the TGAI that are not required but were submitted were: 870.3050 (28 day oral toxicity-rat; MRID 47923564); 870.3050 (28 day oral toxicity-mouse; MRID 47923565); 870.41000 (Chronic oral-dog, MRID 47923570); 870.5550 (Unscheduled DNA synthesis, MRID 47923589); 870.7600 (Dermal penetration, MRID 47923632), Non-guideline (Enzyme induction, MRID 47923593 and MRID 47923599); Non-guideline (S-phase, MRID 47923596, 4792398, and

4792397); Non-guideline (Thyroid hormone, MRID 47923594); Non-guideline (Perchlorate discharge assay, MRID 47923595).

Toxicity studies for impurities (Reg No. 54210775, Reg No. 5356469, Reg No. 5425764)

Toxicity studies for impurities were also submitted. These were:

- Reg No. 54210775: 870.5100 (Bacterial reverse mutation assay, MRID MNRID 47923574); 870.5300 (*In vitro* mammalian cell assay, MRID 47923581); 870.5395 (In vivo mouse micronucleus, MRID 27923586).
- Reg No. 5356469: 870.5100 (Bacterial reverse mutation assay, MRID MNRID 47923575); 870.5300 (*In vitro* mammalian cell assay, MRID 47923582); 870.5395 (In vivo mouse micronucleus, MRID 27923587).
- Reg No. 5425764: 870.5100 (Bacterial reverse mutation assay, MRID 47923576); 870.5300(*In vitro* mammalian cell assay, MRID 47923583); 870.5395 (In vivo mouse micronucleus, MRID 27923588).

Toxicity studies for metabolites (M700F01, M700F02, M700F048)

Toxicity studies for metabolites were also submitted. These were:

- MF700F01: 870.1100 (acute oral toxicity-rat, MRID 47923607), 870.3100 (90-day oral toxicity-rat, MRID 47923608), 870.3700 (developmental toxicity-rabbit, MRID 47923613), 870.5100 (Bacterial reverse mutation assay, MRID 47923609); 870.5300 (*In vitro* mammalian mutation, MRID 47923611); 870.5375 (*In vitro* chromosomal aberration, MRID 47923610); 870.5395 (In vivo mouse micronucleus, MRID 47923612).
- MF700F02: 870.1100 (acute oral toxicity-rat, MRID 47923614), 870.3050 (28-day oral-rat, MRD 47923615); 870.3100 (90-day oral toxicity-rat, MRID 47923616), 870.3700 (developmental toxicity-rabbit, MRID 47923622), 870.5100 (Bacterial reverse mutation assay; MRID 47923617); 870.5300 (*In vitro* mammalian mutation, MRID 47923619);870.5375 (*In vitro* chromosomal aberration, MRID 47923618); 870.5395 (In vivo mouse micronucleus, MRID 47923620).
- M700F048: 870.1100 (acute oral toxicity-rat, MRID 47923623), 870.3050 (28-day oral-rat, MRD 47923624); 870.3700 (developmental toxicity-rabbit, MRID 47923631), 870.5100 (Bacterial reverse mutation assay, MRID 47923625); 870.5300 (*In vitro* mammalian mutation, MRID 47923627); 870.5375 (*In vitro* chromosomal aberration, MRID 47923626); 870.5395 (In vivo mouse micronucleus, MRID 47923628), 870.7485 (metabolism and pharmacokinetics, MRID 47923557), and a non-guideline study (unscheduled DNA synthesis-MRD 47923629).

2. Toxicology Data Requirements (CFR 158.500) for food use of fluxapyroxad (BAS 700F)

		CFR Code for Food Use	Submitted?	MRID No(s).
870.1100	Acute oral toxicity - rat	R	Y	47923558
870.1200	Acute dermal toxicity	R	Y	47923559
870.1300	Acute inhalation toxicity - rat	R	Y	47923560
870.2400	Primary eye irritation - rabbit	R	Y	47923562
870.2500	Primary dermal irritation	R	Y	47923561
870.2600	Dermal sensitization	R	Y	47923563
870.6100	Delayed neurotoxicity (acute) - hen	CR	N	NA
870.6200	Acute neurotoxicity - rat	R	Y	47923605
870.3100	90–day Oral – rodent (rat)	R	Y	47923567
870.3150	90–day Oral - non-rodent (dog)	R	Y	47923569
870.3200	21/28–day Dermal	R	Y	47923571
870.3250	90–day Dermal	CR	N	NA
870.3465	90–day Inhalation - rat	CR	N	NA
870.6100	28–day Delayed neurotoxicity-hen	CR	N	NA
870.6200	90–day Neurotoxicity - rat	R	Y	47923606
870.4100	Chronic oral - rodent	R	Y	47923591
870.4200	Carcinogenicity - two rodent species - rat and mouse preferred	R	Y	47923591 (rat) 47923592 (mouse)
870.3700	Prenatal Developmental toxicity - rat and rabbit, preferred	R	Y	47923603 (rat) 47923604 (rabbit)
870.3800	Reproduction and fertility effects	R	Y	47923602
870.6300	Developmental neurotoxicity	CR	N	NA
870.5100	Bacterial reverse mutation	R	Y	47923572

	assay			47923573
870.5300 870.5375	*In vitro* mammalian cell assay	R	Y	47923580 47923577
870.5385 870.5395	*In vivo* cytogenetics	R	Y	47923584
870.7485	Metabolism and pharmacokinetics	R	Y	47923555 47923556
870.7200	Companion animal safety	CR	N	NA
870.7600	Dermal penetration	CR	Y	47923632
870.7800	Immunotoxicity	R	Y	47923633

R= Required, CR=conditionally required, *=missing, NA=not applicable

3. Bibliography of the Submitted Toxicology Studies

47923558 Sire, G. (2008) BAS 700 F: Acute Oral Toxicity in Rats: Acute Toxic Class Method. Project Number: 2008/1002441/OCR, 10A0683/059045/OCR, 34746/TAR. Unpublished study prepared by Centre International de Toxicologie. 29 p.

47923559 Sire, G. (2008) BAS 700 F: Acute Dermal Toxicity in Rats. Project Number: 2008/1002442/OCR, 11A0683/059048/OCR, 34747/TAR. Unpublished study prepared by Centre International de Toxicologie. 30 p.

47923560 Ma-Hock, L.; Landsiedel, R. (2008) BAS 700 F: Acute Inhalation Toxicity Study in Wistar Rats: 4 Hour Dust Exposure. Project Number: 2008/1074154/OCR, 13I0683/057032/OCR. Unpublished study prepared by BASF Aktiengesellschaft, Experimental Toxicology and Ecology. 35 p.

47923562 Bauer, B.; Landsiedel, R. (2008) BAS 700 F: Acute Eye Irritation in Rabbits. Project Number: 2008/1014225/OCR, 11H0683/052354/OCR. Unpublished study prepared by BASF Aktiengesellschaft, Experimental Toxicology and Ecology. 25 p.

47923561 Remmele, M.; Hellwig, J. (2008) LS 5094351: Acute Dermal Irritation/Corrosion in Rabbits (Including Amendment No. 1). Project Number: 2008/7020134/OCR, 18H0683/052209/OCR. Unpublished study prepared by BASF Aktiengesellschaft, Experimental Toxicology and Ecology. 28 p.

47923563 Gamer, A.; Landsiedel, R. (2008) BAS 700 F: Maximization Test in Guinea Pigs. Project Number: 2008/1014226/OCR, 30H0683/052352/OCR. Unpublished study prepared by BASF Aktiengesellschaft, Experimental Toxicology and Ecology. 41 p.

47923605 Kaspers, U.; Kaufmann, W.; Fabian, E.; et al. (2009) BAS 700 F - Acute Oral Neurotoxicity in Wistar Rats; Administration via Gavage. Project Number: 2009/1065774/US/OCR, 61S0683/05102, 2009/1065774. Unpublished study prepared by BASF SE. 379 p.

47923567 Kamp, H.; Strauss, V.; Groeter, S.; et al. (2009) BAS 700 F: Repeated Dose 90-Day Oral Toxicity Study in Wistar Rats: Administration in the Diet. Project Number: 2007/1005069/OCR, 50C0683/05064/OCR. Unpublished study prepared by BASF Aktiengesellschaft, Experimental Toxicology and Ecology. 448 p.

47923568 Kamp, H.; Strauss, V.; Groeters, S.; et al. (2009) BAS 700 F: Repeated Dose 90-Day Oral Toxicity Study in C57BL/6 J Rj Mice Administration in the Diet. Project Number: 2007/1018641/OCR,

51C0683/05070/OCR. Unpublished study prepared by BASF Aktiengesellschaft, Experimental Toxicology and Ecology. 292 p.

47923569 Hempel, K.; Strauss, V.; Groters, S.; et al. (2009) BAS 700 F: Repeated Dose 90-Day Oral Toxicity Study in Beagle Dogs: Administration in the Diet. Project Number: 2008/1013661/OCR, 31D0683/05084/OCR. Unpublished study prepared by BASF Aktiengesellschaft, Experimental Toxicology and Ecology. 357 p.

47923606 Kaspers, U.; Strauss, V.; Kaulmann, W.; et al. (2009) BAS 700 F - Repeated Dose 90-Day Oral Neurotoxicity Study in Wistar Rats; Administration in the Diet (Including Amendment No. 1). Project Number: 2009/7006263/OCR, 63S0683/05090, 2009/7006263. Unpublished study prepared by BASF SE. 424 p.

47923591 Buessen, R.; Strauss, V.; Groeters, A.; et al. (2009) BAS 700 F: Combined Chronic Toxicity/Carcinogenicity Study in Wistar Rats: Administration Via the Diet up to 24 Months. Project Number: 2009/1072490/OCR, 80C0683/05071/OCR. Unpublished study prepared by BASF Aktiengesellschaft, Labor fuer Oekotoxicologie. 1779 p.

47923592 Buesen, R.; Strauss, V.; Kuettler, K.; et al. (2010) BAS 700 F: Carcinogenicity Study in C57BL/6 J Rj Mice: Administration Via the Diet Over 18 Months (Including Amendment No. 1). Project Number: 2010/7003500/OCR, 87C0683/05082/OCR. Unpublished study prepared by BASF Aktiengesellschaft, Experimental Toxicology and Ecology. 2182 p.

47923603 Buesen, R.; Strauss, V.; Kaufmann, W.; et al. (2009) BAS 700 F - Prenatal Developmental Toxicity Study in Wistar Rats - Oral Administration (Gavage). Project Number: 2009/1072492/US/OCR, EU/30R0683/05094, 2009/1072492. Unpublished study prepared by BASF SE. 385 p.

47923604 Buesen, R.; Fabian, E.; Ravenzwaay, B. (2009) BAS 700 F - Prenatal Developmental Toxicity Study in Himalayan Rabbits - Oral Administration (Gavage). Project Number: 2009/1072493/US/OCR, 40R0683/05089, 2009/1072493. Unpublished study prepared by BASF SE. 279 p.

47923602 Schneider, S.; Strauss, V.; Groeters, S.; et al. (2009) BAS 700 F - Two-Generation Reproduction Toxicity Study in Wistar Rats - Administration via the Diet. Project Number: 2009/1072491/US/OCR, EU/70R0683/05092, 70R0683/05092. Unpublished study prepared by BASF SE. 971 p.

47923572 Schulz, M.; Landsiedel, R. (2008) BAS 700 F: Salmonella typhimurium/Escherichia coli Reverse Mutation Assay (Standard Plate Test and Preincubation Test). Project Number: 2008/1028479/OCR, 40M0683/054184/OCR. Unpublished study prepared by BASF Aktiengesellschaft, Experimental Toxicology and Ecology. 52 p.

47923573 Schulz, M.; Landsiedel, R. (2009) BAS 700 F: Salmonella typhimurium / Escherichia coli Reverse Mutation Assay (Standard Plate Test and Preincubation Test). Project Number: 2009/1080768/OCR, 40M0683/054204/OCR. Unpublished study prepared by BASF Aktiengesellschaft, Experimental Toxicology and Ecology. 52 p.

47923577 Schulz, M.; Landsiedel, R. (2008) BAS 700 F: In vitro Chromosome Aberration Assay in V79 Cells. Project Number: 2007/1023153/OCR, 32M0683/054166/OCR. Unpublished study prepared by BASF Aktiengesellschaft, Experimental Toxicology and Ecology. 92 p.

47923580 Schulz, M.; Landsiedel, R. (2009) BAS 700 F: In Vitro Gene Mutation Test in CHO Cells (HPRT Locus Assay). Project Number: 2009/1078663/OCR, 50M0683/054205/OCR. Unpublished study prepared by BASF Aktiengesellschaft, Experimental Toxicology and Ecology. 57 p.

47923584 Schulz, M.; Landsiedel, R. (2006) Cytogenetic Study in vivo with LS 5094351 in the Mouse Micronucleus Test After Two Oral Administrations. Project Number: 2006/1032708/OCR,

26M0683/054160/OCR. Unpublished study prepared by BASF Aktiengesellschaft, Experimental Toxicology and Ecology. 51 p.

47923555 Fabian, E.; Landsiedel, R. (2009) Carbon 14-BAS 700 F: Study on the Biokinetics in Rats. Project Number: 2009/1074879/OCR, 02B0759/066004/OCR. Unpublished study prepared by BASF Aktiengesellschaft, Experimental Toxicology and Ecology. 104 p.

47923556 Schopfer, C.; Labib, S. (2009) The Metabolism of Carbon 14-BAS 700 F in Wistar Rats. Project Number: 2009/1019789/OCR, 267316/OCR. Unpublished study prepared by BASF Aktiengesellschaft. 467 p.

47923633 Kaspers, U.; Strauss, V.; Groeters, S.; et al. (2009) BAS 700 F - Immunotoxicity Study in Male C57BL/6 J Rj Mice; Administration in the Diet for 4 Weeks. Project Number: 2009/1072494/US/ocr, 683/05105//EU/352759, 43S0683/05105. Unpublished study prepared by BASF SE. 169 p.

47923632 Fabian, E.; Landsiedel, R. (2010) (Carbon 14)-BAS 703 02 F - In-Vivo Dermal Absorption in the Rat. Project Number: 2010/1009626/US/ocr, EU/01B0651/096010, 2010/1009626. Unpublished study prepared by BASF SE. 46 p.

4. New Chemical Screen

Chemical Name: BAS 700 F	PC Code: 138009

Study	MRID	Study Parameter				
		GLP[a]	Test Article[b]	Dosing[c]	Animal Observations[d]	Control Data[e]
870.3100-rat	47923567	Y	Y	Y	Y	NA
870.3150-dog	47923569	Y	Y	Y	Y	NA
870.6200-acute-rat	47923605	Y	Y	Y	Y	Y
870.6200 chronic-rat	47293606	Y	Y	Y	Y	Y
870.3700a-rat	47923603	Y	Y	Y	Y	Y
870.3700b-rabbit	47923604	Y	Y	Y	Y	Y
870.3800-rats	47923602	Y	Y	Y	Y	Y
870.4100-rat	See 870.4200*	Y	Y	Y	**NO (no motor activity, grip strength, reactivity-but not seen at 90 days)**	Y
870.4200-rat	47923591	Y	Y	Y	Y	Y
870.4200-mouse	47923592	Y	Y	Y	Y	Y
870.5100	47923572	Y	Y	Y	Y	Y
	47923573	Y	Y	Y	Y	Y
870.5300	47923580	Y	Y	Y	Y	Y
870.5375	47923577	Y	Y	Y	Y	Y
870.5395	47923584	Y	Y	Y	Y	Y
870.7485	47923555	Y	Y	Y	Y	NA
	47923556	Y	Y	Y	Y	NA
870.7600	47923622	Y	Y	Y	Y	NA
870.7800	47923633	Y	Y	Y	Y	Y

4. Preliminary Hazard Characterization of BAS 700F

4.1 Acute Toxicity

Table 4.1 Acute Toxicity Profile for Fluxapyroxad (BAS 700F)				
Guideline No.	**Study Type**	**MRID(s)**	**Results (Based on Study Report Prior to EPA Review)**	**Toxicity Category**
870.1100	Acute oral [rat]	47923558	LD_{50}>2000 mg/kg	III
870.1200	Acute dermal [rat]	47923559	LD_{50}>2000 mg/kg	III
870.1300	Acute inhalation [rat]	47923560	LD_{50}>5.1 mg/L/4 hr	IV
870.2400	Acute eye irritation [rabbit]	47923562	Non-irritant	IV
870.2500	Acute dermal irritation [rabbit]	47923561	Slight irritant	IV
870.2600	Skin sensitization [guinea Pig]	47923563	Non-sensitizer	NA

NA=Not applicable

4.2 Acute neurotoxicity and subchronic neurotoxicity

	Target Organs	**Most sensitive species?**	**NOAEL/LOAEL (Based on study report)**	**MRID No(s).**
870.6200 Acute neurotoxicity – rat 0, 100, 500, 2000, 6000 ppm (9, 43.7, 176, 530 ♂ 9.4, 47.8, 183, 531 ♀)	brain		NOAEL = 125 mg/kg (♂,♀) Based on neurobehavioral effects (decreased number of rearings, reduced motor activity at day 0) at 500 mg/kg	47923605
870.3050 28 day oral toxicity-rat 0, 100, 500, 2000, 6000 ppm (9, 43.7, 176, 530 ♂ 9.4, 47.8, 183, 531 ♀)	liver		NOAEL = 9 mg/kg (♂) and 47.8 mg/kg (♀) Based on clinical chemistry changes, liver weight increases, and hepatocellular hypertrophy at 43.7 mg/kg (♂) and 183 mg/kg (♀	47923564
870.3050 28 day oral toxicity-mouse 0, 500, 2500, 7000 ppm	liver		LOAEL = 112 mg/kg (♂) and 150 mg/kg (♂) Based on clinical	47923565

(112, 552, 1452 ♂ 150, 746, 2100 ♀)			chemistry changes and/or liver weight increases at all doses. NOAEL not identified.	
870.3100 90–day Oral – rat 0, 100, 500, 2000, 6000 ppm (6.1, 31.2, 126, 407 ♂ 7.3, 35.1, 144, 424 ♀)	liver		NOAEL = 6.1 mg/kg (♂) and 7.3 mg/kg (♀) Based on clinical chemistry changes, liver weight increases, and hepatocellular hypertrophy at 31.2 mg/kg (♂) and 35.1 mg/kg (♀)	47923567
870.3100 90–day Oral – mouse 0, 100, 400, 2000, 6000 ppm (21, 77, 390, 1136 ♂ 32, 128, 610, 1657 ♀)	liver		. NOAEL = 21 mg/kg (♂) and 128 mg/kg (♂) Based on clinical chemistry changes and/or liver weight increases at 77 mg/kg (♂) and 610 mg/kg (♀) .	47923568
870.3150 90–day Oral - non- rodent-dog 0, 300, 1500, 10000 (♂) / 7500 ppm (♀) (9, 45, 295 ♂ 10, 51, 238 ♀)	liver		NOAEL = 9 mg/kg (♂) and 10 mg/kg (♂) Based on clinical chemistry changes at 45 mg/kg (♂) and 51 mg/kg (♀)	47923569
870.3200 21/28–day Dermal 0, 100, 300, 1000 mg/kg	NA		NOAEL = 1000 mg/kg, the highest dose tested. No adverse effects at any dose	47923571
870.3250 90–day Dermal	NA			
870.3465 90–day Inhalation - rat	NA			
870.6100 28–day Delayed neurotoxicity-hen	NA			
870.6200 90–day Neurotoxicity – rat	NA		No signs of neurotoxicity. Neurotoxicity	47923606

0, 200, 1000 and 5000 ppm (11.5, 58, 302 ♂ 13.4, 67, 338 ♀)			NOAEL = 302 mg/kg (♂) and 338 mg/kg (♀), the highest dose tested	
870.4100 Chronic oral – rat 0, 50, 250, 1500, 3000 ppm (2.1, 11, 68, 145 ♂ 2.7, 14, 82, 182 ♀)	systemic		Systemic NOAEL = 2.1 mg/kg (♂) and 2.7 mg/kg (♀); based on decreased body weight and/or clinical chemistry changes at 11 mg/kg (♂) and 14 mg/kg (♀).	47923591
870.4100 Chronic oral – dog 0, 300, 1500, 12000 (♂)/ 9000 (♀) ppm (8, 39, 335 ♂ 9, 43, 257 ♀)	liver		NOAEL = 8 mg/kg (♂) and 9 mg/kg (♀); based on iron storage in spleen and liver, fibrosis of the liver, and/or clinical chemistry changes at 39 mg/kg (♂) and 43 mg/kg (♀)	47923570
870.4200 Carcinogenicity – rat 0, 50, 250, 1500, 3000 ppm (2.1, 11, 68, 145 ♂ 2.7, 14, 82, 182 ♀)	liver		NOAEL = 2.1 mg/kg (♂) and 14 mg/kg (♀); based on hepatocellular adenomas (and carcinomas) at 11 mg/kg (♂) and 82 mg/kg (♂).	47923591
870.4200 Carcinogenicity -- mouse 0, 150, 750, 3000, 6000 ppm (21, 107, 468, 996 ♂ 33, 158, 652, 1307 ♀)	liver		No evidence of carcinogenicity. Systemic NOAEL = 21 mg/kg (♂) and 33 mg/kg (♀); based on increased liver weights and/or hepatocellular fatty changes at 107 mg/kg (♂) and 158 mg/kg (♀).	47923592
870.3700 Prenatal Developmental	Liver/thyroid		Developmental NOAEL =	47923603

toxicity - rat 0, 100, 300, 1000 mg/kg bw/d			1000 mg/kg, highest dose tested Maternal NOAEL = 200 mg/kg; based on liver and thyroid weight changes and thyroid follicular hypertrophy	
870.3700 Prenatal Developmental toxicity – rabbit 0, 10, 25, 60 mg/kg bw/d	systemic		Developmental NOAEL = 25 mg/kg; based on increased incidence of paw hyperflexion at 60 mg/kg Maternal NOAEL = 25 mg/kg; based on clinical signs, abortion, decreased food consumption and body weight effects at 60 mg/kg	47923604
870.3800 Reproduction and fertility effects	Liver/thyroid		Fertility NOAEL = 300 mg/kg, the highest dose tested Developmental NOAEL = 10 mg/kg; based on body weight changes in F1 offspring at 50 mg/kg Parental NOAEL = 10 mg/kg; based on body weight changes, organ weight changes in liver and thyroid, accompanied by histopathological findings at 50 mg/kg	47923602
870.5100 Bacterial reverse mutation assay 20-100-500-	NA		Negative	47923572 47923573

2500-5000 µg/plate				
870.5300 *In vitro* mammalian cell assay 5-6.3-10-12.5-20-25-50-75-100 µg/mL	NA		Negative	47923589
870.5375 *In vitro* chromosomal aberration 3.1-6.3-12.5-25-50-100-200-400 µg/mL	NA		Negative	47923577
870.5385 *In vivo* cytogenetics 0-500-1000-2000 mg/kg bw	NA		Negative	47923584
870.5550 Unscheduled DNA synthesis in vivo 0-1000-2000 mg/kg bw	NA		Negative	47923589
870.7485 Metabolism and pharmacokinetics	NA		Rapid absorption and excretion of BAS 700 F. The parent is metabolized via hydroxylation at the biphenyl ring, conjugation with glucuronic acid or with glutathione-derivatives.	47923555 47923556
870.7200 Companion animal safety	NA			
870.7600 Dermal penetration BAS 703 02F 1670, 33.4, 5.6 µg/cm^2 8, 24, 120 h	NA		DAF= 7.81%	47923632,
870.7800 Immunotoxicity-mouse 0, 500, 2000 and 6000 ppm 106 , 450 and 1323 mg/kg bw/d,	NA		No test-substance related immunotoxic effects at any dose	47923633
Non-guideline Enzyme Induction 0, 250, 1500, 3000 ppm	NA		≥250 ppm: increased total CYP, EROD, PROD, BROD,	47923593

for 14 days; 0, 3000 ppm for 14 days followed by 28-day recovery			MUF-GT and HOBI-GT activities ≥1500 ppm: Increased T-4-UDP-GT	
Non-guideline Enzyme Induction 0, 50 ppm for 14 days;	NA		Males: 50 ppm: Increased BROD and HOBI-GT No effects on total CYP or EROD, PROD, MUF-GT and T4-UDP-GT Females: 50 ppm: Increased BROD, No effects on total CYP or EROD, PROD, MUF-GT, HOBI-GT and T4-UDP-GT	47923599
Non-guideline S-Phase 0, 250, 1500, 3000 ppm for 7, 28, 91 days; 0, 3000 ppm for 28 days followed by 28-day recovery	NA		Males: ≥1500 ppm: Increased cell proliferation at day 7, decreased at day 28 and 91 to control, or slightly above control levels Females: ≥250 ppm: Increased cell proliferation at day 7, decreased at day 28 and 91, but still above control levels	47923596
Non-guideline S-Phase 0, 50, 250, 1500, 3000 ppm for 1, 3, 7, 14 days	NA		Males: ≥1500 ppm: Increased cell proliferation at day 3 and 7, decreased at day 14 to slightly above control levels (No effects on cell proliferation at day 1). Females: ≥50 ppm: Increased cell proliferation at day 3 and 7, decreased at day 14, but still above control levels (No effects on cell proliferation at day 1)	4792398
Non-guideline	NA		Males and Females:	4792397

S-phase 0, 50 ppm for 7, 28, 91 days			No effects on cell proliferation	
Non-guideline Thyroid hormone 0, 50, 250, 1500 and 3000 ppm	NA		Males: 3000 ppm: Increased TSH; decreased T4 Females: 3000 ppm: Increased TSH	47923594
Non-guideline Perchlorate Discharge Assay 0, 3000 ppm	NA		Males and females: Increase in specific 125I activity in thyroid, but no significant iodide discharge after perchlorate injection - indicate an indirect effect on the thyroid	47923595

5. Preliminary Hazard Characterization of Impurities

	Target Organs	Most sensitive species?	NOAEL/LOAEL (Based on study report)	MRID No(s).
Reg No. 54210775				
870.5100 Bacterial reverse mutation assay 2 - 500 µg/plate for all strains except E. coli WP2, which was tested at 20 - 5000 µg/plate			Negative	47923574
870.5300 *In vitro* mammalian cell assay 3.1 - 100 µg/mL without S-9 mix 6.3 - 150 µg/mL with S-9 mix			Negative	47923581
870.5395 In vivo mouse micronucleus 15 - 60 mg/kg bw			Negative	47923586
Reg.No. 5356469				
870.5100 Bacterial reverse mutation assay 20 - 5000 µg/plate			Negative	47923575
870.5300 *In vitro* mammalian cell assay 3.1 - 250 µg/mL without S-9 mix 6.3 - 750 µg/mL with S-9 mix			Negative	47923582
870.5395 In vivo mouse micronucleus 500 - 2000 mg/kg bw			Negative	47923587

Reg.No. 5425764				
870.5100 Bacterial reverse mutation assay 20 - 5000 µg/plat			Negative	47923576
870.5300 *In vitro* mammalian cell assay 6.3 - 450 µg/mL without S-9 mix 25 - 450 µg/mL with S-9 mix			Negative	47923583
870.5395 In vivo mouse micronucleus 500 - 2000 mg/kg bw			Negative	47923588

6. Preliminary Hazard Characterization of Metabolites

	Target Organs	**Most sensitive species?**	**NOAEL/LOAEL (Based on study report)**	**MRID No(s).**
M700F001				
870.1100 Acute oral toxicity-rat			LD50 > 2000 mg/kg bw	47923607
870.3100 90–day Oral – rat 0, 100, 300, 1000 mg/kg bw/d			NOAEL=1000 mg/kg bw LOAEL=not observed	47923608
870.3700 Prenatal development-rabbit 0, 40, 100, 250 mg/kg bw/d			NOAEL maternal=250 mg/kg/bw NOEAL developmental = 250 mg/kg/bw	47923613
870.5100 Bacterial reverse mutation assay 10 - 5000 µg/plate with/without S-9 mix			Negative	47923609
870.5300 *In vitro* mammalian cell			Negative	47923611

assay 250 - 2000 µg/mL With/without S-9 mix				
870.5375 *In vitro* chromosomal abberration			Negative	47923610
870.5395 In vivo mouse micronucleus 500 - 2000 mg/kg bw bw			Negative	47923612
M700F002				
870.1100 Acute oral toxicity-rat			LD50 > 2000 mg/kg bw	47923614
870.3050 28-day oral-rat 0, 1500, 5000, 15000 ppm			NOAEL=1000 ppm LOAEL=not observed	47923615
870.3700 Prenatal development-rabbit 0, 100, 300, 1000 mg/kg bw/d			NOAEL maternal = 300 mg/kg/bw LOAEL maternal= 100 mg/kg/bw based on Clinical signs, mortality, abortions, decreased food consumption and body weight NOAEL developmental = 1000 mg/kg/bw	47923622
870.3100 90–day Oral – rat 0, 100, 300, 1000 mg/kg bw/d			NOAEL=1000 mg/kg bw LOAEL=not observed	47923616
870.5100 Bacterial reverse mutation assay 20 - 5000 µg/plate with/without S-9 mix			Negative	47923617
870.5300 *In vitro* mammalian cell assay 500 - 1650 µg/mL without S-9 mix 125 - 1650 µg/mL With -9 mix			Negative	47923619

870.5375 *In vitro* chromosomal abberration 100-1600 µg/mL with/without S-9 mix			Negative	47923618
870.5395 In vivo mouse micronucleus 375-1500 mg/kg bw			Negative	47923620
M700F048				
870.1100 Acute oral toxicity-rat			LD50 > 2000 mg/kg bw	47923623
870.3050 28-day oral-rat 0, 1500, 5000, 15000 ppm			NOAEL=1000 ppm LOAEL=not observed	47923624
870.3700 Prenatal development-rabbit 0, 10, 30, 100 mg/kg bw/d			NOAEL maternal = 30 mg/kg/bw LOAEL maternal = 100 mg/kg/bw based on Clinical signs, abortions, decreased food consumption and body weight gain NOAEL developmental = 100 mg/kg bw	47923631
870.5100 Bacterial reverse mutation assay 20 - 5000 µg/plate with/without S-9 mix			Negative	47923617
870.5300 *In vitro* mammalian cell assay 500 - 1650 µg/mL without S-9 mix 125 - 1650 µg/mL With -9 mix			Negative	47923619
870.5375 *In vitro* chromosomal abberration 100-1600 µg/mL with/without S-9 mix			Negative	47923618
870.5395 In vivo mouse micronucleus			Negative	47923620

375-1500 mg/kg bw				
870.7485 Metabolism and pharmcokinetics			After single oral administration, 14C-M700F048 was rapidly absorbed from the gastrointestinal tract and metabolized. The excretion of radioactivity was independent from gender and nearly complete after 48 hours. Most of the radioactivity was excreted via the feces, while only small amounts were found in urine.	47923557

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R183668

Chemical Name: 1H-Pyrazole-4-carboxamide, 3-(difluoromethyl)-1-methyl-N-(3',4'5'-trifluoro[1,1'-biphenyl]-2-yl)-

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