UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

February 22, 2012

SUBJECT: **Fluxapyroxad** Human Health Risk Assessment for Use of New Active Ingredient on Cereal Grains, Legume Vegetables (Succulent And Dry), Oil Seed Crops (Canola And Sunflower), Peanuts, Pome Fruit, Stone Fruit, Root And Tuber Vegetables (Potatoes And Sugar Beets), Fruiting Vegetables, And Cotton.

PC Code: 138009
Decision No.: 431203

Petition No.: 0F7709
Risk Assessment Type: Single Chemical Aggregate
TXR No.: NA
MRID No.: NA

DP Barcode: 376616
Registration No.: 7969-GRE, 7969-GNA, 7969-GNT, 7969-GNI, 7969-GNO, 7969-GRN, 7969-GRR
Regulatory Action: Section 3 Registration
Case No.: NA
CAS No.: 907204-31-3
40 CFR: 180.###

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This document provides the Health Effects Division's (HED's) risk assessment for the proposed use of the new active ingredient fluxapyroxad on a wide range of food and seed commodities.

TABLE OF CONTENTS

1.0 EXECUTIVE SUMMARY

This assessment provides information to support a Section 3 registration for the use of the new active ingredient, fluxapyroxad on cereal grains, legume vegetables, oil seed crops, peanuts, pome fruit, stone fruit, root and tuber vegetables, fruiting vegetables, and cotton. This document addresses the exposures and estimated risk associated with the proposed new uses of fluxapyroxad. It provides an assessment of proposed tolerances (pesticide residue limits in food) to ensure that they meet the safety standard established by the Food Quality Protection Act (FQPA) of 1996. This assessment was conducted as part of a global review involving the U.S., Canada, and Australia.

Use Profile

Fluxapyroxad (3-(difluoromethyl)-1-methyl-*N*-(3′,4′,5′-trifluoro[1,1′-biphenyl]-2-yl)-1*H*-pyrazole-4-carboxamide) is a fungicide belonging to the carboxamide class of chemicals. It is a new active ingredient proposed for use on a wide range of crops to control a broad spectrum of fungal diseases. Fluxapyroxad is a pyrazole carboxamide. The mode of pesticidal action as a fungicide is inhibition of succinate dehydrogenase in complex II of the mitochondrial respiratory chain, resulting in inhibition of spore germination, germ tubes, and mycelial growth. Applications may be made using groundboom, airblast, aerial, and standard slurry or mist-type seed treatment equipment. There are no fluxapyroxad products proposed for homeowner use and there are no products proposed for application to residential areas. Recommended tolerances for combined residues of fluxapyroxad and its major metabolites in/on plant and animal commodities range from 0.003 ppm to 20 ppm.

BASF Corporation is requesting a Section 3 registration of four fluxapyroxad products. The products are proposed for use on various seed and food crops. The technical product to be registered is XEMIUM Technical (7969-GRE). The proposed formulations are BAS 700 01 F Fungicide (7969-GNA, an emulsifiable concentrate (EC) containing 5.96% fluxapyroxad); BAS 700 02 F (7969-GNT, for seed treatment, 28.78% ai); BAS 700 03 F (7969-GNI, for seed treatment, 28.70%; BAS 700 04 F (7969-GNO, EC formulation with 26.55% ai); and two co-active ingredient products with pyraclostrobin: BAS 703 01 F (7969-GRN, with fluxapyroxad at 21.26% (2.09 lb ai/gal) and pyraclostrobin at 21.26 %) and BAS 703 02 F (7969-GRR, with fluxapyroxad 14.33% and pyraclostrobin at 28.58%). Crop applications may be begin at emergence, but typical applications begin as plants touch across rows. Maximum single application rates range from 0.09 lbs ai/A for most crops to 0.18 lb ai/A for dry shelled beans. Maximum seasonal application rates range from 0.18 to 0.36 lb ai/A. Proposed pre-harvest intervals (PHIs) are 0 days for pome and stone fruit crops, 21 days for cereal grains and 7 days for other commodities. A 365 day plant back interval (PBI) is required for all crops that are not on the label.

Hazard Identification

An extensive toxicity database for fluxapyroxad was submitted to the Agency for registration of fluxapyroxad. This database is sufficient for hazard characterization and endpoint selection for the anticipated routes (oral, dermal, and inhalation) and durations of exposure (acute, subchronic, and chronic) for the proposed uses.

The primary target organ for fluxapyroxad exposure via the oral route is the liver with secondary toxicity in the thyroid for rats only. Liver toxicity was observed in rats, mice, and dogs, with species differences in both the time of onset, sensitivity, and nature of effects. Rats were the most sensitive species for all durations of exposure. In rats, adaptive effects of hepatocellular hypertrophy and increased liver weights and changes in liver enzyme activities were first observed. As the dose or duration of exposure to fluxapyroxad increased, clinical chemistry changes related to liver function also occurred, followed by hepatocellular necrosis, neoplastic changes in the liver, and tumors. Thyroid effects were observed only in rats. These effects were secondary to changes in liver enzyme regulation, which increased metabolism of thyroid hormone, resulting changes in thyroid hormones, thyroid follicular hypertrophy and hyperplasia, and thyroid tumor formation. Tumors were not observed in species other than rats or in organs other than the liver and thyroid. The Agency classified fluxapyroxad as "not likely" to cause tumors in humans based on convincing evidence that carcinogenic effects are not likely below a defined dose range. This classification was based on a full panel of *in vitro* and *in vivio* studies that showed no evidence of genotoxicity, together with mechanistic studies in the liver and thyroid of rats that satisfied stringent criteria for establishing tumorgenic modes of action.

No evidence of neurotoxicity was observed in response to repeated administration of fluxapyroxad. An acute neurotoxicity study showed decreased rearing and motor activity. This occurred on the day of dosing only in the absence of histopathological effects or alterations in brain weights. This indicated that any neurotoxic effects of fluxapyroxad are likely to be transient and reversible due to alterations in neuropharmacology and not from neuronal damage. No evidence of reproductive toxicity was observed. Developmental effects observed in both rats and mice (thyroid follicular hypertrophy and hyperplasia in rats and decreased defecation, food consumption, body weight/body weight gain, and increased litter loss in rabbits) occurred at the same doses as those that caused adverse effects in maternal animals, indicating no quantitative susceptibility. Since the maternal toxicities of thyroid hormone perturbation in rats and systemic toxicity in rabbits likely contributed to the observed developmental effects there is low concern for qualitative susceptibility. An immunotoxicity study in mice showed no evidence of immunotoxic effects from fluxapyroxad.

The Agency has determined that the quantification of risk using a non-linear approach (i.e., RfD) will adequately account for all chronic toxicity, including carcinogenicity, that could result from exposure to fluxapyroxad.

Fluxapyroxad acute toxicity to mammals is low by all routes of exposure.
No hazards were identified for exposures via the dermal route in dermal toxicity studies. Oral

studies were extrapolated for assessment of inhalation hazards, since no repeated-dose inhalation studies were available. However, an inhalation study is not required at this time.

Dose Response Assessment

Toxicological points of departure (PODs) were selected for dietary/drinking water and occupational exposure scenarios for this assessment. Acute and chronic reference doses (RfDs) were selected for assessment of food and drinking water exposures. The population adjusted dose (PAD) is equivalent to the reference dose (RfD) divided by the additional FQPA Safety Factor, which was reduced to 1X. An acute RfD/PAD for all populations was selected from an acute neurotoxicity study in rats based on decreased motor activity and decreased rearing. A chronic RfD/PAD for all populations was selected from a chronic toxicity/carcinogenicity study in rats based on non-neoplastic changes in the liver (foci, masses). A POD for short-term inhalation exposure was selected from 28 day dietary study in rats based on thyroid effects (thyroid follicular hypertrophy/hyperplasia). A POD for intermediate-term inhalation exposure was selected from a 90 day dietary study in rats based also on thyroid effects. PODs for short- and intermediate-term dermal exposure were not selected because there was no systemic toxicity up to the limit dose in the 28-day dermal toxicity study in rats. An uncertainty factor of 100x was applied to endpoints selected for all exposure routes (10x for interspecies extrapolation, 10x for intraspecies variation).

Exposure/Risk Assessment and Risk Characterization

Dietary (food and water) and occupational exposure and risk assessments were conducted for cereal grains, legume vegetables, oil seed crops, peanuts, pome fruit, stone fruit, root and tuber vegetables, fruiting vegetables, and cotton. Worker inhalation exposures were assessed for handler and post-application activities. Screening level acute and moderately refined chronic dietary and drinking water risk assessments for fluxapyroxad show that dietary and drinking water exposure estimates for the proposed uses are below HED's level of concern for the general population and all population subgroups. Occupational exposure and risk estimates indicate that worker handler and post-application exposures are not of concern at the maximum allowable application rates for the proposed new uses.

Use of Human Studies

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies, listed in Appendix D, have been determined to require a review of their ethical conduct. Some of these studies are also subject to review by the Human Studies Review Board. All of the studies used have received the appropriate review.

2.0 HED RECOMMENDATIONS

2.1 Data Deficiencies/Conditions of Registration

A revised Section F must be submitted. The Agency is denying the registrant's requested tolerance for subgroup 1A. For future consideration of a tolerance for subgroup 1A, field trials on carrot and radish must be submitted. BASF Methods L0137/01 and L0140/02 will be submitted to the Analytical Chemistry Laboratory (ACL), and to FDA for updating PAM II, and to USDA for enforcement of tolerances in livestock commodities. The label must be revised as indicated in Section 2.3 below.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

The residue analytical methods available for enforcement of fluxapyroxad tolerances include the LC/MS/MS method used for data gathering and proposed for enforcement. This method uses reversed-phase HPLC with gradient elution, and includes 2 ion transitions to be monitored for the parent fluxapyroxad.

2.2.2 International Harmonization

There are no Codex MRLs established for residues of fluxapyroxad in any commodities. International harmonization is not an issue at this time.

2.2.3 Recommended Tolerances

Pending submission of a revised Section B (see requirements under Directions for Use), and a revised Section F (see requirements under Proposed Tolerances), there are no residue chemistry issues that would preclude granting a Section 3 registration for the requested uses of fluxapyroxad, or establishment of tolerances for residues of fluxapyroxad as follows:

> Tolerances are established for residues of fluxapyroxad, including its metabolites and degradates, in or on the commodities in Table 1. Compliance with the tolerance levels specified below is to be determined by measuring only fluxapyroxad [3-(difluoromethyl)-1-methyl-*N*-(3′,4′,5′-trifluoro[1,1′-biphenyl]-2-yl)-1*H*-pyrazole-4-carboxamide] in or on the commodity.

Table 1. Proposed and Recommended Tolerances for Fluxapyroxad

Crop Group or Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments; *Correct Commodity Definition*
Apple, wet pomace	3.5	2	
Barley, bran	6	--	Calculated tolerance level (3.0 ppm) is the same as the Grain, Cereal, Group 15 tolerance,

Table 1. Proposed and Recommended Tolerances for Fluxapyroxad			
Crop Group or Commodity	**Proposed Tolerance (ppm)**	**Recommended Tolerance (ppm)**	**Comments; *Correct Commodity Definition***
			so it is not needed.
Beet, sugar	--	0.1	Although there are not sufficient data to establish a tolerance on crop group 1A, there are no data deficiencies that would preclude the unconditional registration of sugar beets.
Beet, sugar, dried pulp	0.16	0.1	
Beet, sugar, tops	4	7	
Cattle, fat	0.1	0.05	Rounded to 0.05 ppm.
Cattle, kidney	0.01	--	Covered by tolerance in/on meat byproducts
Cattle, liver	0.1	--	Covered by tolerance in/on meat byproducts
Cattle, meat	0.01	0.01	
Cattle, meat byproducts	0.1	0.03	
Corn, field, grain	0.1	0.01	
Corn, oil, refined	0.05	0.03	*Corn, oil*
Corn, pop, grain	--	0.01	Separate tolerance is needed because there is more than a 10x difference between the needed tolerance and the crop group tolerance.
Corn, sweet, kernels plus cobs with husks removed	--	0.015	Separate tolerance is needed because there is more than a 10x difference between the needed tolerance and the crop group tolerance.
Cotton, undelinted seed	0.01	0.01	
Cotton, gin byproducts	0.01	0.01	
Egg	0.01	0.002	
Fruit, pome, group 11	0.7	0.8	
Fruit, stone, group 12	1.4	2	
Goat, fat	0.1	0.05	
Goat, kidney	0.01	--	Covered by tolerance in/on meat byproducts
Goat, liver	0.1	--	Covered by tolerance in/on meat byproducts
Goat, meat	0.01	0.01	
Goat, meat byproducts	0.1	0.03	
Grain, aspirated fractions	16.0	6	
Grain, cereal, group 15, except field corn grain	2.5	3	*Grain, cereal, group 15 (except field corn, except wheat)* More than 10x difference: wheat 0.3 ppm, sorghum 0.7 ppm, barley 2 ppm, rice 3 ppm, sweet corn 0.15 ppm; wheat will be excluded from crop group as well.
Grain, cereal, forage, fodder and straw, group 16	25	20	More than 10x difference – corn forage 2 ppm, corn stover 5 ppm, wheat forage 10 ppm, wheat hay 15 ppm, wheat straw, 15 ppm, sorghum forage 4 ppm, stover 2 ppm, barley hay 15 ppm, barley straw 20 ppm, rice straw 2 ppm. However, crop group tolerance will be set as is.
Hog, fat	0.01	--	*Swine, fat* – not needed – Category 3
Hog, liver	0.01	--	*Swine, liver*– not needed – Category 3
Hog, meat	0.01	--	*Swine, meat*– not needed – Category 3

Table 1. Proposed and Recommended Tolerances for Fluxapyroxad			
Crop Group or Commodity	**Proposed Tolerance (ppm)**	**Recommended Tolerance (ppm)**	**Comments; *Correct Commodity Definition***
Hog, meat byproducts	0.01	--	*Swine, meat byproducts*– not needed – Category 3
Horse, fat	0.1	0.05	
Horse, kidney	0.01	--	Covered by tolerance in/on meat byproducts
Horse, liver	0.1	--	Covered by tolerance in/on meat byproducts
Horse, meat	0.01	0.01	
Horse, meat byproducts	0.1	0.03	
Milk	0.02	0.005	
Milk, fat	0.1	--	A milk tolerance was established to harmonize with PMRA. A milk fat tolerance is/is not required because milk fat is account for through the milk tolerance.
Oilseeds, group 20	0.6	0.9	Highest residue in canola was 0.84 ppm, rounded to 0.9 ppm
Peanut	0.02	0.01	
Peanut, refined oil	0.06	0.02	
Peanut, meal	0.03	--	Not needed, only 1.5x concentration
Plum, prune	4	3	
Potato, wet peel	0.2	0.1	
Poultry, byproducts	0.01	--	Not needed – estimated residues more than 10x lower than LOQ (Category 3)
Poultry, fat	0.01	--	Not needed – estimated residues more than 10x lower than LOQ (Category 3)
Poultry, liver	0.01	--	Not needed – estimated residues more than 10x lower than LOQ (Category 3)
Poultry, meat	0.01	--	Not needed – estimated residues more than 10x lower than LOQ (Category 3)
Poultry, skin	0.01	--	Not needed – estimated residues more than 10x lower than LOQ (Category 3)
Rapeseed, (cultivars/varieties and/or hybrids including canola and crambe	0.60	--	not needed, included in oilseeds, group 20
Rice, bran	4.5	4.5	
Rice hulls	10	8	*Rice, hulls*
Sheep, fat	0.1	0.03	
Sheep, kidney	0.01	0.01	Covered by tolerance in/on meat byproducts
Sheep, liver	0.1	0.02	Covered by tolerance in/on meat byproducts
Sheep, meat	0.01	0.01	
Sheep, meat byproducts	0.1	0.03	
Soybean, hulls	6.5	0.3	
Soybean, seed	0.2	0.15	
Sunflower, seed	0.60	--	Not needed, included in oilseed, group 20
Vegetable, Foliage of legume, group 7	18	30	
Vegetables, Fruiting,	0.6	0.7	

Table 1. Proposed and Recommended Tolerances for Fluxapyroxad			
Crop Group or Commodity	**Proposed Tolerance (ppm)**	**Recommended Tolerance (ppm)**	**Comments; *Correct Commodity Definition***
group 8			
Vegetable, legume, dried shelled (except soybean) subgroup 6C	0.35	0.4	*Pea and bean, dried shelled, except soybean, subgroup 6C*
Vegetable, legume, edible podded, subgroup 6A	1.4	2	
Vegetable, legume, succulent shelled, subgroup 6B	0.45	0.5	*Pea and bean, succulent shelled, subgroup 6B*
Vegetable, root, subgroup 1A	0.1	--	*Beet, sugar.* Data was only submitted for sugar beets. No data were submitted for the other two representative commodities of the crop subgroup (carrot and radish). A crop subgroup tolerance is not possible. Field trial data for carrot and radish are also required to establish a crop group tolerance.
Vegetable, tuberous and corm, subgroup 1C	0.04	0.02	
Vegetable, tuberous and corm, except potato, subgroup 1D	0.04	--	Tolerance on this subgroup is not needed since all commodities are included in subgroup 1C
Wheat, bran	6	0.6	
Wheat, germ	3	--	Not needed, concentration is only 1.5x
Wheat, grain	--	0.3	Tolerance is set separately from crop group tolerance because residues in wheat grain are more than 5x lower than the highest residue.

2.2.4 Revisions to Petitioned-For Tolerances

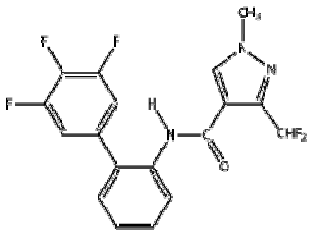
As noted in section 2.2.3 HED has recommended for different tolerances than proposed by the registrant. HED has used the OECD calculator to determine the appropriate tolerances.

2.3 Label Recommendations

The label must be revised to delete use on root and tuber vegetables, subgroup 1A. Only use on sugar beets from subgroup 1A is allowed. The petitioner must clarify the PHI for peanuts. The 365 day plant back interval must remain on the label.

3.0 INGREDIENT PROFILE

3.1 Chemical Identity

TABLE 2. Fluxapyroxad Test Compound Nomenclature.	
Chemical structure	
Common name	Fluxapyroxad (ISO, proposed)
Company experimental name	BAS 700 F
IUPAC name	3-(difluoromethyl)-1-methyl-*N*-(3′,4′,5′-trifluorobiphenyl-2-yl)pyrazole-4-carboxamide
CAS name	3-(difluoromethyl)-1-methyl-*N*-(3',4',5'-trifluoro[1,1'-biphenyl]-2-yl)-1*H*-pyrazole-4-carboxamide
CAS #	907204-31-3
Molecular Formula	$C_{18}H_{12}F_5N_3O$
End-use product/EP	Xemium Technical, BAS 700 01F, BAS 700 02F, BAS 700 03F, BAS 700 04F

3.2 Physical/Chemical Characteristics

A detailed description of the physiciochemical properties of fluxapyroxad is provided in Appendix C. Fluxapyroxad exhibits relatively low solubility in water and higher solubility in organic solvents. It has a very low vapor pressure (6.1×10^{-11} Torr at 25° C). Fluxapyroxad is persistent in terrestrial and aquatic environments and is moderately to slightly mobile in soil. Fluxapyroxad does not present significant concerns for bioaccumulation based on the lipophilicity of the compound and on results of bioconcentration studies in fish.

3.3 Pesticide Use Pattern

Fluxapyroxad is a fungicide belonging to the carboxamide class of chemicals. It is a new active ingredient proposed for use on a wide range of crops to control a broad spectrum of fungal diseases. Product registrations and proposed use patterns and formulations are provided in Table 3.

Table 3. Summary of Directions for Use of Fluxapyroxad					
Applic. Timing, Type, and Equip.	**Formulation**	**Applic. Rate (lb ai/A)**	**Max. No. Applic. per Season**	**Max. Seasonal Applic. Rate (lb ai/A)**	**PHI (days)**
Cereal Grains					
Foliar spray Ground, Aerial or Chemigation	5.96% EC 26.55% EC 21.26% EC 14.33% EC	0.09	2	0.18	21
Use Directions and Limitations: A minimum 7-day RTI is specified. Applications may be begin at emergence, but typical applications begin as plants touch across rows. A 7 day PHI is allowed for sweet corn only.					
Seed Treatment	28.7% SC	0.01	Not provided	Not applicable	Not applicable
Use Directions and Limitations: Rate is expressed in lb ai/100 lb seed. Apply in enough water to ensure adequate coverage, but without damaging the seed. A higher rate of 0.02 lb ai/100 lb seed is allowed on sweet corn and sorghum seed. A higher rate of 0.05 lb ai/100 lb seed is allowed on wheat seed.					
Cotton, Sunflower					
Seed Treatment	28.7% SC	0.0103	Not provided	Not applicable	Not applicable
Use Directions and Limitations: Rate is expressed in lb ai/100 lb seed. Apply in enough water to ensure adequate coverage, but without damaging the seed. A higher rate of 0.02 lb ai/100 lb seed is allowed on sweet corn and sorghum seed. A higher rate of 0.05 lb ai/100 lb seed is allowed on wheat seed.					
Oilseeds, Dried Shelled Peas, Soybeans					
Foliar spray Ground, aerial or chemigation	5.96% (0.52 lb/gal) EC 26.55% (2.47 lb/gal) EC 21.26% (2.09 lb/gal) EC 14.33% (1.39 lb/gal) EC	0.09	2	0.18	7
Use Directions and Limitations: A minimum 7-day RTI is specified. Applications may be begin at emergence, but typical applications begin as plants touch across rows. DO NOT harvest for forage, green chop, vines, or hay within 7 days of last application (14 days for 1.39 and 2.09 lb/gal EC). Do not feed soybean hay for 14 days after application (21 days for 2.09 lb/gal EC). No livestock feeding restrictions for oilseeds.					
Dried Shelled Beans					
Foliar spray Ground, aerial or chemigation	5.96% (0.52 lb/gal) EC 26.55% (2.47 lb/gal) EC 21.26% (2.09 lb/gal) EC 14.33% (1.39 lb/gal) EC	0.18	2	0.36	7
Use Directions and Limitations: A minimum 7-day RTI is specified. Applications may be begin at emergence, but typical applications begin as plants touch across rows. DO NOT harvest for forage, green chop, vines, or hay within 7 days of last application (14 days for 1.39 and 2.09 lb/gal EC).					
Edible Podded Legume Vegetables, Succulent Shelled Beans and Peas					
Foliar spray Ground, aerial or chemigation	5.96% (0.52 lb/gal) EC 26.55% (2.47 lb/gal) EC 21.26% (2.09 lb/gal) EC 14.33% (1.39 lb/gal) EC	0.09	2	0.18	7
Use Directions and Limitations: A minimum 7-day RTI is specified. Applications may be begin at emergence, but typical applications begin as plants touch across rows. DO NOT harvest for forage, green chop, vines, or hay within 7 days of last application (14 days for 1.39 and 2.09 lb/gal EC).					
Fruiting Vegetables Group, Sugar Beets, Tuberous & Corm Vegetables Subgroup					
Foliar spray	5.96% (0.52 lb/gal) EC	0.09	3	0.27	7

Table 3. Summary of Directions for Use of Fluxapyroxad					
Applic. Timing, Type, and Equip.	**Formulation**	**Applic. Rate (lb ai/A)**	**Max. No. Applic. per Season**	**Max. Seasonal Applic. Rate (lb ai/A)**	**PHI (days)**
Ground, aerial or chemigation	26.55% (2.47 lb/gal) EC 21.26% (2.09 lb/gal) EC 14.33% (1.39 lb/gal) EC				
Use Directions and Limitations: A minimum 7-day RTI is specified (14 days for sugar beets). Apply a minimum of 20 gallons of spray volume per acre, and increase the spray volume as the plants grow during the season. Spray volume should be proportional to the amount of plant tissue to be covered such that 100 gallons of spray per acre is used on mature plants. DO NOT make more than two (2) consecutive applications of fluxapyroxad before alternating to a labeled fungicide with a different mode of action. Sugar beet leaves, roots and tops may be fed no sooner than 7 days after last application. Use of the 2.09 lb/gal EC on sugar beets is not permitted.					
Peanut					
Foliar spray Ground, aerial or chemigation	5.96% (0.52 lb/gal) EC 26.55% (2.47 lb/gal) EC 14.33% (1.39 lb/gal) EC	0.09	3	0.27	7
Use Directions and Limitations: A minimum 14-day RTI is specified. DO NOT make more than two (2) consecutive applications of fluxapyroxad before alternating to a labeled fungicide with a different mode of action. Do not graze or harvest for peanut forage. The 1.39 lb/gal EC label states that a 7 day PHI is required in the crop specific use directions, and 14 days in the overview table.					
Pome Fruit Group					
Foliar spray Ground, aerial or chemigation	5.96% (0.52 lb/gal) EC 26.55% (2.47 lb/gal) EC 21.26% (2.09 lb/gal) EC 14.33% (1.39 lb/gal) EC	0.09	4	0.36	0
Use Directions and Limitations: Do not use less than 10 gallons of spray solution per acre. A minimum 7-day RTI is specified. DO NOT make more than two (2) consecutive applications of fluxapyroxad before alternating to a labeled fungicide with a different mode of action. No restriction on livestock grazing or feeding.					
Stone Fruit Group					
Foliar spray Ground, aerial or chemigation	5.96% (0.52 lb/gal) EC 26.55% (2.47 lb/gal) EC 21.26% (2.09 lb/gal) EC 14.33% (1.39 lb/gal) EC	0.11	3	0.33	0
Use Directions and Limitations: Do not use less than 10 gallons of spray solution per acre. A minimum 7-day RTI is specified. DO NOT make more than two (2) consecutive applications of fluxapyroxad before alternating to a labeled fungicide with a different mode of action.					

3.4 Anticipated Exposure Pathways

Dietary (food and water) and occupational exposures via dermal and inhalation pathways are expected based on proposed uses of fluxapyroxad on a variety of food commodities. Acute and chronic dietary exposure and risk assessments were conducted for the proposed uses. HED assessed occupational exposure and risk from proposed uses of fluxapyroxad for seed and foliar applications on cereal grains, sorghum, legume vegetables (succulent and dry), oil seed crops (canola and sunflower), peanuts, pome fruit, stone fruit, root and tuber vegetables (potatoes and sugar beets), fruiting vegetables, and cotton. Worker exposures were assessed for handler and

post-application activities. There are no residential uses for fluxapyroxad so residential exposure to children via incidental oral activities is not anticipated.

3.5 Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf).

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas postapplication are evaluated. Further considerations are currently in development, as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 HAZARD CHARACTERIZATION/ASSESSMENT

4.1 Toxicology Studies Available for Analysis

An extensive toxicity database for fluxapyroxad was submitted to the Agency for registration of fluxapyroxad. Submitted studies via the oral route cover durations and endpoints relevant for hazard characterization for acute and chronic dietary assessments. These studies include metabolism and pharmacokinetic studies, subchronic and chronic dietary studies in rats, mice, and dogs; prenatal developmental studies in rats and rabbits, a 2-generation reproduction and fertility effects study in rats, acute and subchronic neurotoxicity studies in rats, an immunotoxicity study in mice, a complete battery of *in vitro* and *in vivo* genotoxicity studies, and carcinogenicity studies in rats and mice. Supplemental studies were submitted to further investigate the mode of action of fluxapyroxad on the liver and thyroid. These studies, together with a dermal toxicity study and dermal penetration study, are also appropriate for hazard characterization for short-term to intermediate-term exposures via the dermal route. Occupational exposures are also anticipated via the inhalation route, but no subchronic inhalation study was submitted. Therefore, extrapolation from oral studies appropriate for short-term to intermediate-term exposures will be used for inhalation hazard characterization. A subchronic inhalation study is not required at this time. There are no toxicity studies available for fluxapyroxad in the general literature, as it is a new active ingredient.

Acute toxicity studies (acute oral, dermal, and inhalation studies in rats, eye irritation and dermal irritation studies in rabbits, and a skin sensitization study in guinea pigs) were also

submitted for each formulation for labeling purposes that can also inform hazard characterization.

There are three metabolites of fluxapyroxad: two soil metabolites (M700F001 and M700F002) and a metabolite found on food crops (M700F048). There are no toxicity studies of these metabolites in the general literature. However, subchronic dietary studies in rats, prenatal developmental studies in rabbits, and a complete battery of *in vitro* and *in vivo* genotoxicity studies were submitted to the Agency for these metabolites. Metabolism and pharmacokinetic studies were also submitted for the M700F048 plant metabolite. These studies are sufficient for hazard characterization.

4.2 Absorption, Distribution, Metabolism, & Elimination (ADME)

Pharmacokinetic and metabolism studies with radiolabeled fluxapyroxad in rats show that plasma levels of radiolabel scaled with dose, indicating that uptake was not saturated up to dose levels of 500 mg/kg. There were no sex differences observed in the rate or extent of absorption. The time to peak plasma levels (t_{MAX}) was dependent upon on dose, and ranged from 1 hour (at 5 mg/kg) to 24 hours (at 500 mg/kg) with maximum mean plasma concentrations (C_{MAX}) ranging from 1.85/1.57 µg Eq/g to 65.31/66.08 µg Eq/g in males/females. Areas under the curve (AUCs) ranged from 45.4/35.7 µg Eq h/g (at 500 mg/kg) to 4215.2/5667.4 µg Eq h/g (at 5 mg/kg) in males/females. The initial half-life of elimination ranged from 14.5/12.0 h (at 5 mg/kg) to 27.3/24.5 h (at 500 mg/kg) in males/females.

Mass balance, tissue distribution and biliary excretion studies were performed in rats at doses of 150 mg/kg and 7.5 mg/kg. These studies indicated that radioactivity was widely distributed in both sexes within 16 hours, with bioavailability estimated to be between 65-80%. A similar pattern of distribution was observed in males and females: the highest concentrations were found in the gut contents and stomach contents. However, lower concentrations were found in numerous other organs/tissues, including the liver, thyroid, adrenal glands, kidney, pancreas, testes/uterus, and brain. For both male and female rats, radioactivity declined in all tissues over time. The time course of the amount of radioactivity found in urine and feces indicated the excretion occurred predominantly within three days after dosing, indicating a low potential for bioaccumulation. For both dose groups, the majority of the radioactivity (84-94%) was excreted via the feces within 168 hours. The amount excreted via the urine during this time was 3-17%. Bile duct cannulation experiments showed that the bile was a major route of excretion, with 51-64% of radioactivity eliminated via this route. Negligible amounts were excreted as expired air in rats. Residue chemistry studies in ruminants indicated that fluxpyroxad and metabolites are excreted in milk.

Metabolism studies revealed that the main biotransformation steps of BAS 700 F in rats are hydroxylation at the biphenyl ring system (sometimes repeatedly), N-demethylation at the pyrazole ring system, loss of a fluorine atom at the biphenyl ring system, and conjugation with glucuronic acid or sulfate, and conjugation with glutathione derivatives. These reactions produced approximately 51 different metabolites. Minor biotransformation steps produced

additional metabolites, including M700F001 (from hydrolysis of the amide bond between the pyrazole and biphenyl rings) and M700F002 (from N-demethylation of M700F001). These metabolites were also found in soil, as described below.

No information was provided on the pharmacokinetics and metabolism of the soil metabolite M700F001 or impurities. Pharmacokinetic studies in rats showed that the soil metabolite M700F002 was systemically bioavailable and distributed to the bone marrow, blood and liver after oral administration. Pharmacokinetic and metabolism in rats on the plant metabolite M700F048 also showed systemic bioavailability with distribution to the bone marrow, blood, and liver after administration via the oral route. Excretion was primarily via the feces in both sexes, and was rapid (within 12-24 hours of dosing).

A dermal penetration study was submitted by the registrant that utilized the BAS 703 02 F formulation, which contains both fluxapyroxad and pyraclostrobin (BAS 500F). The Agency calculated a dermal absorption factor of 8.4% at dose of 5.6 $\mu g/cm^2$ for potential use in future risk assessments.

4.3 Toxicological Effects

In mammals, the primary target organ for fluxapyroxad exposure via the oral route is the liver. Liver toxicity in response to fluxapyroxad via the oral route was observed in several species: rats, mice, and dogs. The sensitivity to liver toxicity and the development and manifestations of liver toxicity over time varied with species. In rats, the most sensitive species, adaptive effects of hepatocellular hypertrophy and increased liver weights and changes in liver enzyme activities were first observed. As the dose or duration of exposure to fluxapyroxad increased, clinical chemistry changes related to liver function were observed, followed by hepatocellular necrosis and neoplastic liver changes (foci, masses), which were considered adverse effects. Liver toxicity was also observed in mice and dogs. In subchronic studies in mice, increased liver weights were observed along with fatty changes in the liver, with few observations of hepatocellular hypertrophy. At higher doses, liver necrosis was also observed. Liver effects in subchronic studies in dogs were limited to increased liver weights at high doses. However, in chronic studies, increased liver weights were observed in conjunction with fibrosis and cirrhosis.

Fluxapyroxad administration via the oral route resulted in toxic effects in the thyroid. These thyroid effects occurred secondary to the effects on the liver and were seen only in rats. Thyroid effects in rats were observed throughout the toxicity database and included changes in serum thyroid hormone levels, enlarged thyroid, increased thyroid weights, and/or microscopic effects of thyroid follicular hypertrophy and hyperplasia. These effects showed a clear threshold, were evident within weeks and were observed out to two years. Although these effects were observed in male and female rats, males were usually more sensitive. Threshold doses at which thyroid effects occurred in the rat were accompanied by changes in the liver that were considered adaptive or potentially adverse. These changes included increased liver weights, hepatocellular hypertrophy, and changes in liver-associated clinical chemistry parameters. These results

suggested that the effects in the thyroid were secondary to fluxapyroxad-induced changes in thyroid hormone metabolism by the liver and not due to direct action of fluxapyroxad on the thyroid. Supplementary studies (including a perchlorate discharge assay and measurement of T_4-metaboilizing Phase II enzyme activities) confirmed indirect thyroid effects. The most sensitive of these thyroid effects are perturbations in thyroid hormone levels, which occur temporally before histopathological alternations in the thyroid.

Chronic oral administration of fluxapyroxad resulted in treatment-related liver tumors in male and female rats and thyroid tumors in male rats only. No tumors were observed in male or female mice. Also, no evidence of mutations or chromosomal damage were observed in a panel of guideline *in vitro* assays, and no evidence of chromosomal damage was observed in a guideline mouse erythrocyte micronucleus study *in vivo*. Together, these data indicated that the thyroid and liver tumors observed in rats were due to non-genotoxic and/or species-related factors and not due to genotoxic effects. Supplemental studies supporting non-genotoxic modes of action for liver and thyroid tumors also indicated clear thresholds protective for tumorgenic effects.

Although the primary effects of oral fluxapyroxad exposure were on the thyroid and liver, effects in other organ systems were also noted. However, the doses at which these other effects occurred exceeded those of the liver and thyroid effects. Treatment-related effects of decreased rearing (in males only) and decreased motor activity (in both sexes) were observed after dosing via oral gavage in the acute neurotoxicity study. These effects were considered equivocal for neurotoxcity, since they may indicate transient and reversible neurotoxicity from a bolus exposure and/or general malaise. There were no neurotoxic effects observed in the subchronic dietary toxicity study. Fluxapyroxad did not cause reproductive toxicity in rats. Developmental toxicity in rats was limited to decreased body weight and body weight gain in offspring and was observed at the same dose levels that caused thyroid dysregulation in parental animals. Developmental toxicity in rabbits was limited to paw hyperflexion, a malformation that usually reverses as the animal matures, and was observed at the same dose levels that caused reduced maternal body weight. There were clear NOAELs for these developmental effects.

An unusual effect of tooth whitening was observed was observed in rats in several studies. This effect was observed with increasing oral doses of fluxapyroxad. This was likely due to decreased deposition of a yellow iron-containing pigment in the "outer outer enamel" layer of the teeth. Bone thickening and white discoloration of the skull bones were also observed, as was increased deposition of Perl's Prussian Blue stain (indicative of iron) in other bone tissues. These effects in the teeth and bones suggested treatment-related changes in iron storage, but there was no evidence of microscopic damage to these tissues or clinical evidence of compromised tissue function. . The Agency considered the potential for flurosis to result from any fluoride released during metabolism of fluxpyroxad. The Agency concluded that it is unlikely that fluxapyroxad would cause fluorosis because detailed histopathological evaluation of the teeth did not show changes consistent withfluorosis at the highest dose in parental and F1 males of the rat 2-generation reproduction and fertility effects study.

Immunotoxicity was investigated via the oral route in male mice. No immunotoxic effects of fluxapyroxad were observed at doses up to and including the limit dose.

A dermal toxicity study in rats was the only route-specific study that was submitted for occupational assessments. No toxic effects of fluxapyroxad were observed at doses up to and including the limit dose.

Acute toxicity studies show that fluxapyroxad exhibits low acute toxicity by all exposure routes (EPA Toxicity Category III or IV) and is not a dermal sensitizer.

Subchronic oral toxicity studies in rats, developmental toxicity studies in rabbits, and *in vitro* and *in vivo* genotoxicity studies were performed for fluxapyroxad metabolites F700F001, M700F002, and M700F048. The Agency considers these studies sufficient for hazard identification and characterization. Like fluxapyroxad, no genotoxic effects were observed for any of these metabolites. All three metabolites displayed lower subchronic toxicity via the oral route than fluxapyroxad, with evidence of non-specific toxicity (decreased body weight) observed only for M700F0048 at the limit dose. Only M700F0048 exhibited developmental toxicity at doses similar to those that caused developmental effects in rabbits with fluxapyroxad treatment. However, these effects (abortions and resorptions) were of a different nature than for fluxapyroxad (paw hyperflexion) and are likely secondary to maternal toxicity. These data are sufficient for the Agency to conclude that these metabolites do not have hazards that exceed those of fluxapyroxad in nature, severity, or potency.

The complete toxicity profile for fluxapyroxad is provided in Appendix A.

4.4 Safety Factor for Infants and Children (FQPA Safety Factor)

The FQPA Safety Factor is reduced to 1X. This reduction is based on the availability of a complete toxicity database with clear NOAELs for characterizing neurotoxicity and sensitivity during development, supplemental studies that characterize the effects fluxapyroxad on thyroid hormones, and no residual uncertainties in the exposure data base. The information used to reduce uncertainties in hazard and exposure of infants and children is described in detail below.

4.4.1 Completeness of the Toxicology Database

The Agency considers the toxicity database used to characterize the hazards of fluxapyroxad to infants and children as complete. A 2-generation reproductive and developmental toxicity study in rats and developmental toxicity studies in rats and rabbits are available to assess the quantitative and qualitative susceptibility of the fetus, infants, and children to fluxapyroxad. In addition to these lifestage-specific studies, a full toxicity database of guideline and supplemental studies available in adult animals to evaluate neurotoxicity, immunotoxicity, genotoxicity, and thyroid effects.

4.4.2 Evidence of Neurotoxicity

Acute and subchronic neurotoxicity studies are available for fluxapyroxad. Treatment-related effects of decreased rearing and motor activity were observed only in the acute neurotoxicity study and only on the day of dosing. These effects are equivocal, as they may indicate transient and reversible neurotoxicity and/or general malaise. No developmental neurotoxicity study is available for fluxapyroxad. However, the Agency has considered the potential for fluxapyroxad to cause developmental neurotoxicity as a result of thyroid hormone disruption, which is more sensitive than the endpoints used in a developmental neurotoxicity study. The Agency has evaluated supplemental thyroid hormone data submitted by the registrant and considered the ontogeny of thyroid hormone metabolism to determine that adverse thyroid hormone disruptions in the young are unlikely to occur at dose levels similar to the points of departure chosen for risk assessment. The Agency has low concern for neurotoxic effects of fluxapyroxad at any life stage.

4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

No evidence of quantitative susceptibility was observed in a reproductive and developmental toxicity study in rats or in developmental toxicity studies in rats and rabbits. Developmental toxicity in rats in a 2 generation study was limited to decreased body weight and body weight gain in offspring and was observed at the same dose levels that caused thyroid follicular hypertrophy/hyperplasia in parental animals. However, low birth weights, which can result from thyroid dysregulation in maternal animals, was observed in the first generation only, with no decreased body weights observed in the second generation until lactation day 7. Developmental toxicity in rabbits was limited to paw hyperflexion, a malformation that is not considered to result from a single exposure and that usually reverses as the animal matures. This effect was observed in untreated controls and all treatment groups but was significantly increased only at the high dose at which reduced maternal body weight was also observed. Although these developmental effects differed from the maternal effects and so indicate qualitative susceptibility, these developmental effects are of low concern to the Agency. The Agency's rationale for low concern for developmental toxicity is that these effects were of low severity, were likely secondary to maternal toxicity, and demonstrated clear NOAELs. Nonetheless, the risk assessment is protective of paw hyperflexion because this effect occurs at dose levels higher than the points of departure selected for risk assessment for repeat-exposure scenarios.

4.4.4 Residual Uncertainty in the Exposure Database

There are no residual uncertainties in the exposure database. The residue data base is adequate. The dietary risk assessment is conservative and will not underestimate dietary exposure to fluxapyroxad. There are no residential uses proposed for fluxapyroxad.

4.5 Toxicity Endpoint and Point of Departure Selection

4.5.1 Dose-Response Assessment

Acute and chronic dietary endpoints were selected from acute, subchronic, and chronic oral toxicity studies in the database for fluxapyroxad. The endpoint of decreased motor activity and decreased rearing identified in the acute neurotoxicity study in rats was chosen for the acute dietary endpoint because it is clearly adverse and clearly results from a single exposure. Paw hyperflexion was not considered to be a single-dose effect and thus was not selected for an acute endpoint. No other endpoints in the toxicity database for fluxapyroxad were identified that were likely to result from a single exposure. The endpoint of liver foci and masses identified in the chronic toxicity/carcinogenicity study in rats was chosen for the chronic dietary endpoint. The duration of exposure in this study is appropriate for a chronic dietary endpoint and the point of departure at this endpoint is protective for all adverse effects in rats and other species that occur at higher doses and/or for shorter durations of exposure.

There are no residential uses for fluxapyroxad and so residential risks will not be assessed. However, endpoints were chosen for occupational exposure scenarios. A dermal toxicity study was selected for short-term and intermediate-term dermal scenarios because it is a route-specific study that also assessed all of the endpoints used in the other exposure scenarios and durations of exposure (e.g. neurological endpoints, thyroid and liver histopathology). Although developmental toxicity was not assessed in the dermal toxicity study, the Agency has low concern for developmental toxicity because the only observed effect, paw hyperflexion, was likely secondary to maternal toxicity and is not considered severe, since this effect is usually reversible as the animal matures. No hazard was identified at the limit dose in the dermal toxicity study. No inhalation studies were available for short-term and intermediate-term inhalation scenarios. Therefore, endpoints from oral studies were evaluated. The endpoint of changes in thyroid hormones and thyroid follicular hypertrophy/hyperplasia from the 28-day oral study in rats was identified for short-term inhalation. This is the most sensitive endpoint in the most sensitive species for an adverse effect for a duration of exposure ranging from 1-30 days. The endpoint of thyroid follicular hypertrophy/hyperplasia was identified from the 90 day oral toxicity study in rats for intermediate-term inhalation. This endpoint was chosen because the duration of exposure is relevant to a 1-6 month intermediate-term exposure and this was the most sensitive endpoint in the most sensitive species. Although thyroid hormones were not measured in the dermal study, calculation of dermal equivalency dose from the developmental study and dermal absorption data indicates that a dermal endpoint is not required for this effect.

4.5.2 Recommendation for Combining Exposure Routes

Under FQPA, when there are potential residential exposures to a pesticide, HED must aggregate exposures from three major sources: oral, dermal and inhalation exposures. These combined residential exposures must then be aggregated with exposure from food and water to determine aggregate risk. Since there are no residential incidental oral exposures to fluxapyroxad, aggregate exposure from food and non-food oral exposures is not required.

4.5.3 Cancer Classification

Tumors related to fluxapyroxad treatment were observed in the liver of male and female rats and in the thyroid in male rats only. Males were more sensitive than females to the tumorgenic effects of fluxapyroxad in the liver. The combined incidence of liver adenomas and carcinomas in males ranged from 10% at 11 mg/kg bw/day to 43% at 145 mg/kg bw/day compared to 2% in controls. For females, the combined incidence of adenomas and carcinomas ranged from 8% at 82 mg/kg bw/day to 14% at 182 mg/kg bw/day compared to 2% in controls. Dose and temporal concordance data supported a non-genotoxic mitogenic MOA for liver adenomas and carcinomas in rats. This MOA is based on early changes in liver enzyme regulation and increased cell proliferation that lead to microscopic and macroscopic foci and then to adenoma and carcinoma formation. The endpoint of changes in liver enzyme regulation at 2.1/2.7 mg/kg bw/day in males/females provides a clear threshold for liver tumors.

The incidence of treatment-related combined thyroid follicular adenomas and carcinomas in male rats ranged from 15% at 68 mg/kg bw/day to 18% at 145 mg/kg bw/day compared to 5% in controls. Dose and temporal concordance data supported a MOA for thyroid tumorgenesis in rats in which early changes in liver enzyme regulation lead to dysregulation of thyroid hormone homeostasis, thyroid follicular hypertrophy/hyperplasia, and thyroid tumors. The endpoint of changes in liver enzyme regulation at 2.1/2.7 mg/kg bw/day in males/females provides a clear threshold for thyroid tumors.

In accordance with the EPA's Final Guidelines for Carcinogen Risk Assessment (March, 2005), the CARC classified fluxapyroxad as "Not likely to be Carcinogenic to Humans" based on convincing evidence that carcinogenic effects are not likely below a defined dose range (J. Kidwell, June 9, 2011, TXR 0055930). This decision was based on the following considerations:

(i) No treatment-related tumors were seen in male or female mice when tested at doses that were adequate to assess carcinogenicity (including the Limit Dose);

(ii) Treatment-related liver tumors were seen in male rats at doses $\geq$ 250 ppm (11 mg/kg/day) and in female rats at doses $\geq$ 1500 ppm (82 mg/kg/day);

(iii) Treatment-related thyroid follicular cell tumors were seen in male rats only at doses $\geq$ 1500 ppm (68 mg/kg/day);

(iv) There is no mutagenicity concern from *in vivo* or *in vitro* assays;

(v) The hypothesized mode of action (i.e, a non-genotoxic) for each tumor type (i.e., the liver and thyroid) was supported by adequate studies that clearly identified the sequence of key events, dose-response concordance and temporal relationship to the tumor types. The mode of action met the criteria established by the Agency. The Agency does not have cancer concerns for workers because the proposed use patterns indicate that workers will not be exposed to fluxapyroxad for long enough periods at levels sufficient to induced liver and/or thyroid tumors.

4.5.4 Summary of Points of Departure Used in Risk Assessment

Toxicological doses/endpoints selected for the fluxapyroxad risk assessment are provided in Tables 4 and 5.

Table 4. Summary of Toxicological Doses and Endpoints for Fluxapyroxad for Use in Dietary and Non-Occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty/ FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (General Population, including Infants and Children and Females 13-49 years of age)	NOAEL= 125 mg/kg/day	UF_A= 10 x UF_H=10 x FQPA SF= 1x	Acute RfD = 1.25 mg/kg/day aPAD= 1.25 mg/kg/day	Acute neurotoxicity study in rats LOAEL = 500 mg/kg/day based on decreased motor activity (both sexes) and decreased rearing (males only)
Chronic Dietary (All Populations)	NOAEL= 2.1 mg/kg/day	UF_A= 10 x UF_H=10 x FQPA SF= 1x	Chronic RfD= 0.021 mg/kg/day cPAD = 0.021 mg/kg/day	Chronic toxicity/carcinogenicity study in rats LOAEL = 11 mg/kg/day based on non-neoplastic changes in the liver (foci, masses)
Cancer (oral, dermal, inhalation)	Classification: Not likely to be carcinogenic to humans at doses sufficient to induce liver and/or thyroid tumors.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOA=mode of action.

Table 5. Summary of Toxicological Doses and Endpoints for Fluxapyroxad for Use in Occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal Short-Term (1-30 days)	NOAEL= 1000 mg/kg/day	UF_A=10x UF_H=10x	NA: No hazard identified	28-day dermal toxicity study in rats LOAEL = Not observed
Dermal Intermediate-Term (1-6 months)	NOAEL= 1000 mg/kg/day	UF_A=10x UF_H=10x	NA: No hazard identified	28-day dermal toxicity study in rats LOAEL = Not observed
Inhalation Short-Term (1-30 days)	NOAEL= 9 mg/kg/day	UF_A=10x UF_H=10x	Occupational LOC for MOE = 100	28-day oral toxicity study in rats LOAEL = 176 mg/kg/day based on changes in thyroid hormones and thyroid follicular hypertrophy/hyperplasia
Inhalation Intermediate-term (1-6 months)	NOAEL= 7.3 mg/kg/day	UF_A=10x UF_H=10x	Occupational LOC for MOE = 100	LOAEL = 35.1 mg/kg/day based on thyroid follicular hypertrophy/hyperplasia

Table 5. Summary of Toxicological Doses and Endpoints for Fluxapyroxad for Use in Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty Factors**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Cancer (oral, dermal, inhalation)	Classification: Not likely to be carcinogenic to humans at doses sufficient to induce liver and/or thyroid tumors.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

5.0 DIETARY AND DRINKING WATER EXPOSURE AND RISK ASSESSMENT

5.1 Metabolite/Degradate Residue Profile

5.1.1 Summary of Plant and Animal Metabolism Studies

The nature of the residue in plants and animals is adequately understood. Fluxapyroxad metabolism studies were conducted using an aniline label and a pyrazole label in soybeans, tomato, and wheat; in the rotational crops spinach, radish, and wheat; and in animal studies in goats, hens. The primary residue found in plant and livestock commodities is fluxapyroxad parent. Metabolite residues to be included in the risk assessment are M700F008 and M700F010 for milk residues only.

5.1.2 Summary of Environmental Degradation

Fluxapyroxad does not readily undergo aerobic or anaerobic degradation in soil, with half-lives ranging from 213 to 1,827 days. In terrestrial field dissipation studies, dissipation half-lives ranged from 17 to 436 days and fluxapyroxad was detected infrequently below the top 6 inches of the soil. Fluxapyroxad is moderately to slightly mobile based on adsorption K_{OC} values (496 to 1,424 mL/g_{oc}) in studies conducted on U.S. and foreign soils. Fluxapyroxad is stable to hydrolysis (pH values of 5, 7 and 9) and to soil and aqueous photolysis. Fluxapyroxad has the potential to leach to ground water, particularly where high water tables are present, high rainfall/irrigation occurs, and where sandy soils with low organic matter exist. As previously noted, fluxapyroxad was detected infrequently at depths greater than 6 inches in terrestrial field dissipation studies. However, given its persistence and mobility, the terrestrial field dissipation studies, which only lasted a maximum of 472 days, may not have been long enough to capture leaching over time. Fluxapyroxad does not readily undergo aerobic or anaerobic degradation in aquatic systems, with half-lives of 420 to 731 days. Fluxapyroxad is not expected to volatilize (vapor pressure 6.1 x 10^{-11} Torr at 25˚ C). It will not likely bioaccumulate based on results of bioconcentration studies in fish.

5.1.3 Comparison of Metabolic Pathways

Submitted data shows that fluxapyroxad is metabolized mainly by hydroxylation at the biphenyl moiety (sometimes repeatedly), loss of a fluorine atom at the biphenylring (presumably by substitution with a hydroxyl-group), N-demethylation at the pyrazole moiety, hydrolysis of the amide bond, and oxidation of the difluoromethyl group. Conjugation of the hydroxyl-groups in addition to these reactions led to the observed large number of metabolites. The metabolic pathway of fluxapyroxad is similar in primary and rotational crops but with some variation in metabolite levels. In general, the parent compound is the main residue followed by the metabolites M700F008, M700F002 and M700F048. For livestock, the parent, M700F008, M700F005, M700F004, M700F010 and dimer of the parent were observed as major residues in fat, muscle, milk, liver, kidney and/or egg commodities. In the rat, the parent was the main residue followed by M700F008, and their corresponding metabolites hydroxylated in the biphenyl moiety (M700F009, M700F005, and M700F006). Other reactions led to the formation of a large number of minor metabolites. Metabolite structures are provided in Appendix B.

5.1.4 Residues of Concern Summary and Rationale

HED has concluded that the residue of concern for tolerance expression for all commodities is parent only based on the recommendation of the Residues of Concern Knowledgebase Subcommittee (ROCKS). Although there was concern expressed about metabolites in livestock commodities (particularly M700F008 being present at greater levels than parent in most matrices), for tolerance setting the parent compound alone is adequate as an indicator for misuse.

The ROCKS recommended inclusion of parent fluxapyroxad and M700F008 for risk assessment for primary and rotational crops. While the parent is generally the most significant residue in plants, results from crop field trials with cherries and peppers show a higher relative level of M700F008 with respect to the parent at longer PHIs. The M700F008 metabolite is demethylated parent and is expected to have comparable toxicity to the parent. The major residues observed in the confined rotational studies are parent fluxapyroxad and M700F008, M700F002 and M700F048. The metabolite M700F002 was observed as a major residue in rotational spinach only and was not detected at all in the field studies of accumulation in rotational crops. The metabolite M700F048 was observed as a major residue in radish tops in the confined study, but was seen at much lower levels than the parent and M700F008 in the field studies. Toxicity studies with M700F002 and M700F048 show that these two metabolites are not likely to be more toxic than the parent. For livestock commodities, except milk, the ROCKS recommended that fluxapyroxad and M700F008 be included for risk assessment purposes based on results from metabolism and feeding studies which show that parent fluxapyroxad and M700F008 are the major residues in ruminant and poultry commodities. For milk only, the ROCKS recommended that fluxapyroxad, M700F008 and M700F010 be included for risk assessment purposes based on the metabolism study in goat showed the presence of M700F010 at 12-15% TRR in milk which is highly consumed commodity by children. M700F010 is

hydroxylated parent and likely to have comparable toxicity to the parent. For water, the ROCKS committee recommended including parent fluxapyroxad only in the risk assessment. Parent fluxapyroxad and M700F001 were the only two major residues identified in the environmental fate studies. Although M700F001 was identified as a major degradate, available evidence suggests that this degradate has lower toxicity than the parent and will be present in low concentrations relative to the parent in drinking water.

Table 6: Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression

Matrix		Residues of Concern[1]	
		For Risk Assessment	For Tolerance Expression
Plants	Primary Crop	Fluxapyroxad and M700F008	Fluxapyroxad
	Rotational Crop	Fluxapyroxad and M700F008	Fluxapyroxad
Livestock	Ruminant	Fluxapyroxad, M700F008 and M700F010[2]	Fluxapyroxad
	Poultry	Fluxapyroxad and M700F008	Fluxapyroxad
Drinking Water		Fluxapyroxad	NA

[1] Fluxapyroxad is 3-(difluoromethyl)-1-methyl-*N*-(3′,4′,5′-trifluoro[1,1′-biphenyl]-2-yl)-1*H*-pyrazole-4-carboxamide. M700F008 is 3-(difluoromethyl)-N-(3′,4′,5′-trifluorobiphenyl-2-yl)pyrazole-4-carboxamide. M700F010 is 3-(difluoromethyl)-N-(hydroxy-3',4',5'-trifluoro[1,1'-biphenyl]-2-yl)-1H-pyrazole-4-carboxamide

[2] The metabolite M700F010 will be considered a residue of concern for milk only.

5.2 Food Residue Profile

5.2.1 Residues in Crops

An adequate number and crop field trials conducted in appropriately representative locations are available for fluxapyroxad for the majority of crop applications and use patterns (application rate and PHI) submitted on the label. However, field trials on carrot and radish must be submitted in order to allow use on root and tuber vegetables, subgroup 1A. Submitted field trial data for fluxapyroxad on cereal grains, legume vegetables (succulent and dry), oil seed crops (canola and sunflower), peanuts, pome fruit, stone fruit, root and tuber vegetables (potatoes and sugar beets), and fruiting vegetables reflect the use of 2-4 foliar applications of an emulsifiable concentrate formulation. Decline studies were submitted for each commodity, as required. Seed treatment studies for fluxapyroxad on cotton reflect the use of an SC formulation. Adequate confined and field rotational crop data were provided for fluxapyroxad. The field rotational crop studies show finite residues at 30, 60, 90, and 120 day plant back intervals (PBIs) except for wheat, which is also a primary crop. The confined rotational crop studies show no quantifiable residues at a 365 day plant back interval. Detailed information on residue data from crop field trials on fluxapyroxad and its metabolites is provided in the Residue Chemistry Chapter. (D390223)

5.2.2 Residues in Meat, Milk, Poultry, and Eggs

The magnitude of the residue of fluxapyroxad and metabolites M700F002 and M700F008 in dairy cattle tissues, milk, laying hen tissues and eggs was determined in acceptable feeding studies in dairy cattle and laying hens. Based on these studies, tolerances are needed for

cattle meat, fat, milk products and eggs. Tolerances are not needed for cattle liver and kidney or for any poultry tissues because estimated residues are more than 10x lower than the level of quantitation (LOQ).

5.2.3 Residues in Processed Commodities

Processing studies were provided for processed commodities associated with cereal grains, oil seed crops (canola and sunflower), peanuts, pome fruit, stone fruit, root and tuber vegetables (potatoes and sugar beets), and fruiting vegetables. Concentration was observed in some processed commodities and tolerances are being set in those commodities (see Table 1).

5.2.4 Storage Stability

Adequate storage stability data for fluxapyroxad, per se, are available to support the storage conditions and durations of field trial samples for raw agricultural commodities. The available data indicate that residues of fluxapyroxad are relatively stable for up to 24 months in/on apple (fruit), tomato (fruit), triticale (whole plant), soybean (seed), avocado (fruit), dried pea (seed), cereal (grain), potato (tuber), grape (fruit), lemon (fruit), and wheat (straw) stored at -20 C. Storage stability of metabolite M700F008 was investigated for 24 months. Some instability was seen for the metabolite M700F008 in oily and starchy commodities. Residues of M700F008 have been corrected to account for the 57% recovery in the storage stability studies in oily commodities.

5.3 Water Residue Profile

Drinking water residues were incorporated directly into the acute and chronic dietary analyses as "water, direct, all sources" and "water, indirect, all sources." Estimated Drinking Water Concentrations (EDWCs) for fluxapyroxad were provided by the Environmental Fate and Effects Division (EFED) (D138009, C. Peck, 9/21/11). EFED generated the surface water estimates using the Tier I aquatic model FIRST (FQPA Index Reservoir Screening Tool). Ground water estimates were calculated using the Tier 1 Screening Concentration in Ground Water model (SCIGROW). EDWCs for fluxapyroxad (parent only) were derived based on fluxapyroxad use on dry shelled beans (except soybeans) at 0.18 lbs ai/acre/application, applied 2 times per year with a 7-day reapplication interval for a maximum total annual application rate of 0.36 lb ai/A/yr. Surface and groundwater EDWCs for fluxapyroxad are provided in Table 3. Estimated drinking water residues for peak concentration of 0.014 mg/L (ppm) were used in the acute assessment. Estimated 30 year annual average drinking water concentrations of 0.0067 mg/L (ppm) were used the chronic assessment.

Table 7. EDWCs for the Fluxapyroxad Human Health Risk Assessment

Drinking Water Source	Peak (µg/L)	Annual Mean (µg/L)
Surface Water	14.1	6.7
Ground Water	0.087	0.087

5.4 Dietary and Drinking Water Exposure and Risk

HED conducted screening-level acute and chronic dietary and drinking water exposure and risk assessments using the Dietary Exposure Evaluation Model with the Food Commodity Intake Database (DEEM-FCID™). Dietary risk assessment incorporates both exposure and toxicity of a given pesticide. For acute and chronic dietary assessments, the risk is expressed as a percentage of a maximum acceptable dose (i.e., the dose which HED has concluded will result in no unreasonable adverse health effects). This dose is referred to as the population adjusted dose (PAD). The PAD is equivalent to the reference dose (RfD) divided by the additional FQPA Safety Factor, if applied. For acute and non-cancer chronic exposures, HED is concerned when estimated dietary risk exceeds 100% of the PAD.

5.4.1 Acute Dietary and Drinking Water Exposure and Risk Estimates

A conservative acute dietary exposure analysis was performed for the general population and all population subgroups. Tolerance level residues adjusted to account for the metabolites of concern (M700F008, M700F010) and 100 % crop treated assumptions were used. DEEM default and empirical processing factors were used to modify the tolerance values. The acute analysis incorporated the 1 in 10 year peak surface drinking water estimate from application of fluxapyroxad to dry shelled beans. The resulting 95th percentile acute exposure estimates are not of concern for the general population or for any subgroup population. The 95th percentile acute population adjusted dose (aPAD) for children 1-2 years old, the subgroup with the highest risk estimate, is 6%. The 95th percentile aPAD for the general population is 2%.

Table 8. Summary of Acute Dietary Exposure and Risk for Fluxapyroxad

Population Subgroup	aPAD (mg/kg/day)	Acute (95th Percentile)	
		Exposure (mg/kg/day)	% aPAD
General U.S. Population	1.25	0.023310	2
All Infants (< 1 year old)		0.074082	6
Children 1-2 years old		0.068058	5
Children 3-5 years old		0.047241	4
Children 6-12 years old		0.026755	2
Youth 13-19 years old		0.015850	2
Adults 20-49 years old		0.016730	1
Adults 50+ years old		0.013855	1
Females 13-49 years old		0.014264	1

5.4.2 Chronic Dietary and Drinking Water Exposure and Risk Estimates

A moderately refined chronic dietary exposure analysis was performed for the general U.S. population and various population subgroups. Highest average field trial (HAFT) residues for parent plus metabolite were used for all plant commodities. For livestock commodities tolerance level residues adjusted to account for the metabolites of concern (M700F008, M700F010) were used. An assumption of 100 % crop treated was also used for the chronic dietary analysis. DEEM default and empirical processing factors were used to modify the tolerance values. The chronic analysis incorporated the 10 year average surface drinking water

estimate from application of fluxapyroxad to dry shelled beans. Chronic dietary risk estimates are not of concern for general population or other population subgroups. The population subgroup with the highest risk estimate is children 1-2 years old with a % chronic PAD (cPAD) of 48%. The % cPAD for the general U.S. population is 14%.

Table 9. Summary of Chronic Dietary Exposure and Risk for Fluxapyroxad			
Population Subgroup	**cPAD (mg/kg/day)**	**Chronic**	
		Exposure (mg/kg/day)	**% cPAD**
General U.S. Population	0.022	0.002923	14
All Infants (< 1 year old)		0.008474	40
Children 1-2 years old		0.010055	48
Children 3-5 years old		0.007369	35
Children 6-12 years old		0.004011	19
Youth 13-19 years old		0.002217	11
Adults 20-49 years old		0.002204	11
Adults 50+ years old		0.002007	10
Females 13-49 years old		0.001986	10

6.0 RESIDENTIAL EXPOSURE/RISK CHARACTERIZATION

A residential assessment is not required because there are no fluxapyroxad products proposed for registration for homeowner use and there are no products proposed for application to residential areas.

6.1 Residential Bystander Postapplication Inhalation Exposure

Based on the Agency's current practices, a quantitative residential bystander postapplication inhalation exposure assessment was not performed for fluxapyroxad at this time. However, volatilization of pesticides may be a potential source of postapplication inhalation exposure to individuals nearby to pesticide applications. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009. The Agency received the SAP's final report on March 2, 2010 (http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html). The Agency is in the process of evaluating the SAP report and may, as appropriate, develop policies and procedures, to identify the need for and, subsequently, the way to incorporate postapplication inhalation exposure into the Agency's risk assessments. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative postapplication inhalation exposure assessment for fluxapyroxad.

6.2 Spray Drift

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for fluxapyroxad. The Agency has been working with the Spray Drift Task Force, EPA Regional

Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices (see the Agency's Spray Drift website for more information at http://www.epa.gov/opp00001/factsheets/spraydrift.htm). On a chemical by chemical basis, the Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new database submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift with specific products with significant risks associated with drift.

7.0 AGGREGATE EXPOSURE/RISK CHARACTERIZATION

In accordance with the FQPA, when there are potential residential exposures to a pesticide, aggregate risk assessment must consider exposures from three major routes: oral, dermal, and inhalation. There are three sources for these types of exposures: food, drinking water, and residential uses. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure. The proposed/registered fluxapyroxad uses are not expected to result in residential exposure. Therefore, the acute and chronic exposure estimates provided in the Dietary Exposure Section represent aggregate exposure.

8.0 CUMULATIVE RISK

Section 408(b)(2)(D)(v) of FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

EPA does not have, at this time, available data to determine whether fluxapyroxad has a common mechanism of toxicity with other substances. Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to fluxapyroxad and any other substances and, fluxapyroxad does not appear to produce a toxic metabolite produced by other substances which have tolerances in the U. S. For the purposes of this tolerance reassessment action, therefore, EPA has not assumed that fluxapyroxad has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's OPP concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/fedrgstr/EPA_PEST/2002/January/Day_16/.

9.0 OCCUPATIONAL EXPOSURE/RISK CHARACTERIZATION

9.1 Exposure Scenarios

Occupational handler and post-application exposure scenarios are assessed for the risk assessment of the proposed crop and seed commodities. Based on the product labels and information provided by the registrant, short- and intermediate-term exposure is assessed for occupational handlers and post-application activities. Chronic exposure is not expected for the proposed use patterns. Only inhalation exposures are assessed for proposed new uses of fluxapyroxad. Dermal exposures are not assessed because PODs for short- and intermediate-term dermal exposure were not selected as there was no systemic toxicity up to the limit dose in the subchronic dermal toxicity study in rats. Labels for fluxapyroxad formulations require that mixers, loaders, applicators and other handlers (seed treatment activities) wear long-sleeved shirt and long pants, chemical resistant gloves, protective eyewear, and shoes plus socks.

9.2 Handler Exposure

The term "handler" applies to individuals who mix, load, and apply the pesticide product. There is a potential for exposure to fluxapyroxad during mixing, loading, and application activities through inhalation routes only. Occupational handler exposure is expected for individuals involved in commercial seed treatment (primary handlers), and planting treated seeds (secondary handlers) as well as aerial, flagging, airblast, and groundboom applicators. According to proposed labels, applications may be begin at plant emergence, but typical applications begin as plants touch across rows. The following handler exposure scenarios evaluated for this assessment are based on information provided in the proposed labels.

9.2.1 Handler Exposure Scenarios

9.2.1.1 Mixing and Loading Scenarios

- Open mixing/loading for aerial application;
- Open mixing/loading for groundboom application;
- Open mixing/loading for airblast application.

9.2.1.2 Application Scenarios

- Applying sprays with aerial equipment;
- Applying sprays with groundboom equipment;
- Applying sprays with airblast equipment

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9.2.1.3 Flagging

The Agency has evaluated scenarios that may be limited in nature such as flagging during aerial applications because engineering controls (i.e. Global Positioning Satellite technology) are

now predominantly used as indicated by the 1998 National Agricultural Aviation Association (NAAA) survey of their membership. It appears, however flaggers are still used in approximately 10 to 15 percent of aerial application operations. In cases like these, the Agency strongly encourages the use of the engineering control system, but will continue to evaluate risks for flaggers and any other population where a clear exposure pathway exists until the potential for exposure is eliminated. The Agency is aware that NAAA is conducting another survey of its membership on exposure issues and will consider those results as is timely and appropriate.
For pesticide handlers, HED presents estimates of dermal exposure for "baseline" (i.e. workers wearing a single layer of work clothing consisting of a long sleeved shirt, long pants, shoes, plus socks and no protective gloves, as well as for "baseline" and the use of protective gloves or other personal protective equipment (PPE), as might be necessary. However, dermal exposures were not assessed for this analysis because there was no systemic toxicity up to the limit dose in the subchronic dermal toxicity study in rats. The fluxapyroxad product labels for foliar treatments recommend applicators and other handlers to wear long-sleeved shirt and long pants, and shoes plus socks.

9.2.1.4 Seed Treatment

Occupational seed treatment handlers may experience short- and intermediate-term exposure to fluxapyroxad while performing seed treatment activities in commercial settings. In addition, occupational secondary handlers may experience short- and intermediate-term exposure while planting fluxapyroxad-treated seeds. No chemical-specific handler exposure data were submitted in support of this use pattern. For assessing commercial seed treatment and seed planting activities, unit exposure data were taken from HED ExpoSAC Policy 14: SOPs for Seed Treatment and MRID 47054702. The amount of active ingredient handled depends on the application rate (lb ai/lb seed) and the pounds of seed treated in a day (or the pounds of seed that can be planted in a day), all of which vary depending upon the seed type. Values for the amount of seed treated and planted per day were obtained from HED ExpoSAC Policy 15. The results are presented in Table 5.

<u>Treating Seed (Primary Handler)</u>

Potential occupational exposure scenarios from the use of fluxapyroxad as a commercial seed treatment include:

- Mixing, loading, applying liquid formulations;
- Bagging treated seed;
- Sewing bags; and
- Multiple activities.

Typically, for large-scale commercial seed treatments, workers perform only those specific individual tasks listed above; however, it is assumed that workers also may perform multiple activities throughout the day. As a result a "multiple activities" scenario (i.e. where one worker performs all seed treatment tasks such as loading/applying, sewing, bagging, cleaning,

calibration, repair, forklift driver, etc.) was addressed.

Planting Treated Seed (Secondary Handler)

Potential occupational exposure scenarios from the use of fluxapyroxad as a commercial seed treatment include planting treated seed (secondary handler). Planting treated seed consists of the farmer purchasing bags of treated seed, placing the seed in the hopper and applying seed to fields (considered a secondary handler exposure scenario). The fluxapyroxad product labels discuss inhalation exposures exclusively for mixers, loaders, applicators and other handlers (seed treatment activities) to wear long-sleeved shirt and long pants, chemical resistant gloves, protective eyewear, and shoes plus socks.

9.2.2 Handler Exposure Data

No chemical-specific handler exposure data were submitted in support of this registration. It is HED's policy to use data from the USEPA OPP Occupational Pesticide Handler Unit Exposure Surrogate Reference Table (5/4/11). http://www.epa.gov/pesticides/science/handler-exposure-data.html).

9.2.3 Handler Exposure Assumptions

- Average body weight of an adult handler is 80 kg.
- Exposure duration short-term (1- 30 days), intermediate-term (1-6 months)
- Maximum label application rates for aerial, groundboom and airblast:
  - 0.09 – 0.18 lb ai/A
- Maximum label application rates for seed treatment:
  - 0.01- 0.05 lb ai/100 lb seed
- Area treated for aerial, groundboom and airblast application:
  - 1200 acres per day for aerial application
  - 200 acres per day for groundboom application to corn, soybean and wheat
  - 80 acres per day for groundboom application to all other crops
  - 20 acres per day for airblast application to stone fruit
- Amount (pounds) of Seed Treated per Day (Primary Handler)
  - Beans and Peas (CG6 and CG7) – 194,000
  - Soybean, Sorghum - 718,000
  - Sunflower and safflower - 718,000
  - Cereal Grains (CG 15 and 16) – 718,000
  - Corn (field, sweet, pop) – 550,000
  - Cotton – 160,000
  - Peanut – (Loader/Applicator) = 120,000), (Sewer, Bagger, and Multiple activities = 718,000)
- Amount (pounds) of Seed Treated per Day (Secondary Handler)
  - Beans and Peas (CG6 and CG7) – 194,000
  - Soybean – 20,000

- Sunflower and safflower – 7,700
- Barley – 19,000
- Oat - 26,000
- Triticale – 20,000
- Rye - 24,000
- Wheat – 30,000
- Corn (field, sweet, pop) – 3,000
- Sorghum – 800
- Cotton – 3,600
- Peanut – 11,000
-

9.2.4 Handler Exposure and Risk Estimates

A target LOC or MOE of 100 is considered adequate for inhalation. All worker exposures are assessed as short- and intermediate-term based on label prescribed uses and expected exposure durations. Exposure and risk estimates indicate non-cancer risks are not of concern for occupational handler activities for the proposed new uses (MOEs > 100). Summaries of occupational handler exposure and risk calculations, assumptions, and results are provided in Tables 10, 11 and 12.

Table 10: Short and Intermediate-Term Risk Assessment For Agricultural Uses of Fluxapyroxad

Exposure Scenario	Inhalation Unit Exposure (µg/lb ai)[1]	Crops	Application Rate (lb ai/A)[2]	Area Treated (A/day)[3]	MOE[5]	
					Short-Term	Intermed-Term
					Inhalation	
Mixer/Loader						
Aerial Fixed Wing (enclosed cockpit)	0.219	Fruiting vegetables, oilseed crops (flax, rape, and sunflower seed), pome fruits, stone fruits, sugar beet, tuberous and corn vegetables (incl. Potatoes),oat, peanut, rye, triticale	0.09	350	100,000	85,000
		Dried shelled beans	0.18		52,000	42,000
		corn, soybean, wheat	0.09	1200	30,000	25,000
Groundboom (open Cab)	0.219	Dried shelled beans	0.18	80	230,000	190,000
		Fruiting vegetables, oilseed crops (flax, rape, and sunflower seed), pome fruits, stone fruits, sugar beet, tuberous and corn vegetables (incl. Potatoes),oat, peanut, rye, triticale	0.09		460,000	370,000
		corn, soybean, wheat		200	180,000	150,000
Airblast (open cab)		stone fruits	0.11	40	750,000	610,000
Applying						

Table 10: Short and Intermediate-Term Risk Assessment For Agricultural Uses of Fluxapyroxad						
Exposure Scenario	**Inhalation Unit Exposure (µg/lb ai)[1]**	**Crops**	**Application Rate (lb ai/A)[2]**	**Area Treated (A/day)[3]**	**MOE [5]**	
					Short-Term	**Intermed-Term**
					Inhalation	
Aerial Fixed Wing (enclosed cockpit)	0.068	Fruiting vegetables, oilseed crops (flax, rape, and sunflower seed), pome fruits, stone fruits, sugar beet, tuberous and corn vegetables (incl. Potatoes),oat, peanut, rye, triticale	0.09	350	340,000	270,000
		Dried shelled beans	0.18		170,000	140,000
		corn, soybean, wheat	0.09	1200	98,000	80,000
Groundboom (open Cab) (Chemigation)[6]	0.068	Dried shelled beans	0.18	80	150,000	120,000
		Fruiting vegetables, oilseed crops (flax, rape, and sunflower seed), pome fruits, sugar beet, tuberous and corn vegetables (incl. Potatoes),oat, peanut, rye, triticale	0.09		290,000	240,000
		corn, soybean, wheat		200	120,000	95,000
Airblast (open cab)		Stone fruits	0.11	20	36,000	29,000
Flagging						
Aerial Fixed Wing (enclosed cockpit)	0.35	corn, soybean, wheat[4]	0.09	1200	33,000	26,000

[1] Inhalation unit exposure values represent no respirator.
[2] Application rates are based on maximum values found in proposed labels
[3] Daily area treated is based on the area that can be reasonably applied in a single day for each exposure scenario of concern based on the application method and formulation/packaging type. (standard EPA/OPP/HED values).
[4]Corn, Soybeans, and Wheat have the most conservative MOEs, therefore representative for Flagging activities.
[5] Short-/Intermediate-Term MOE = Inhalation NOAEL (9.0 mg/kg/day or 7.3 mg/kg/day) / Daily Inhalation Dose). The LOC is 100.
[6] Chemigation: Aerial applicator MOEs are protective.
* Daily Dose (mg/kg/day) was calculated by Unit Exposure * 100 % Inhalation absorption factor * Application rate * Area treated} / 70 kg. {Where: inhalation absorption is assumed to be 100%}

Table 11. Short- and Intermediate-Term Primary Handler Exposures and Risks for Fluxapyroxad Seed Treatment						
Seed Type	**Inhal UE[a] mg/lb**	**Max App Rate[b] lb ai/lb seed**	**Amt Treated[c] lb seed/day**	**Inhal Dose[d] mg/kg/day**	**Short-Term Inhal MOE[e]**	**Intermediate-Term Inhal MOE[f]**
Loader/Applicator (No Respirator)						
Peanuts	0.00034	0.0001	5,500	0.000058	180,000	140,000
Dried Shelled Beans	0.00034	0.0001	194,000	0.000094	110,000	89,000
Soybean	0.00034	0.0001	718,000	0.00035	29,000	24,000
Cereal Grains	0.00034	0.0005	718,000	0.00017	5,900	4,800

Table 11. Short- and Intermediate-Term Primary Handler Exposures and Risks for Fluxapyroxad Seed Treatment						
Seed Type	**Inhal UE[a] mg/lb**	**Max App Rate[b] lb ai/lb seed**	**Amt Treated[c] lb seed/day**	**Inhal Dose[d] mg/kg/day**	**Short-Term Inhal MOE[e]**	**Intermediate-Term Inhal MOE[f]**
Corn	0.00034	0.0005	550,000	0.0013	7,700	6,200
Cotton	0.00034	0.0002	160,000	0.00016	66,000	54,000
Sunflower and safflower	0.00034	0.0002	718,000	0.0017	15,000	12,000
Sorghum	0.00034	0.0002	718,000	0.0007	15,000	12,000
Sewer (No Respirator)						
Peanuts	0.00023	0.0001	718,000	0.00024	44,000	35,000
Dried Shelled Beans	0.00023	0.0001	194,000	0.000064	160,000	130,000
Soybean	0.00023	0.0001	718,000	0.00024	44,000	35,000
Cereal Grains	0.00023	0.0005	718,000	0.0012	8,700	7,100
Corn	0.00023	0.0005	550,000	0.0009	11,000	9,200
Cotton	0.00023	0.0002	160,000	0.00011	98,000	79,000
Sunflower and safflower	0.00023	0.0002	718,000	0.00047	22,000	18,000
Sorghum	0.00023	0.0002	718,000	0.00047	22,000	18,000
Bagger (No Respirator)						
Peanuts	0.00016	0.0001	718,000	0.00016	63,000	51,000
Dried shelled Beans	0.00016	0.0001	194,000	0.000044	230,000	190,000
Soybean	0.00016	0.0001	718,000	0.00016	63,000	51,000
Cereal Grains	0.00016	0.0005	718,000	0.00082	13,000	10,000
Corn	0.00016	0.0005	550,000	0.00063	16,000	13,000
Cotton	0.00016	0.0002	160,000	0.000073	140,000	110,000
Sunflower and safflower	0.00016	0.0002	718,000	0.00033	31,000	25,000
Sorghum	0.00016	0.0002	718,000	0.00033	31,000	25,000
Multiple Activities (No Respirator)						
Peanuts	0.0016	0.0001	718,000	0.0016	6,300	5,100
Dried Shelled Beans	0.0016	0.0001	194,000	0.00044	23,000	19,000
Soybean	0.0016	0.0001	718,000	0.0016	6,300	5,100
Cereal Grains	0.0016	0.0005	718,000	0.0082	1,300	1,200
Corn	0.0016	0.0005	550,000	0.0063	1,600	1,300
Cotton	0.0016	0.0002	160,000	0.00073	14,000	11,000
Sunflower and safflower	0.0016	0.0002	718,000	0.0033	3,100	2,500
Sorghum	0.0016	0.0002	718,000	0.0033	3,100	2,500
Planters						
Peanuts	0.0034	0.0001	11,000	0.000047	190,000	210,000
Dried Shelled Beans	0.0034	0.0001	8,000	0.000034	260,000	190,000
Soybean	0.0034	0.0001	20,000	0.000085	110,000	86,000
Cereal Grains	0.0034	0.0005	26,000	0.00011	81,000	66,000
Corn	0.0034	0.0005	3,000	0.000064	140,000	110,000
Cotton	0.0034	0.0002	3,600	0.000031	290,000	240,000
Sunflower and safflower	0.0034	0.0002	800	0.000068	1,300,000	1,100,000
Sorghum	0.0034	0.0002	800	0.000068	1,300,000	1,100,000

a Unit Exposures from HED Exposure Science Advisory Council Policy 14: Standard Operating Procedures for Seed Treatment.

b Application Rates based on proposed label uses for fluxapyroxad.

c HED default for lb seed planted per day from HED Exposure Science Advisory Council Policy 15,
d Daily Inhalation Dose (mg/kg/day) = daily inhalation unit exposure (mg/lb ai) x application rate (lb ai/lb seed) x amount planted (lb seed/day) x absorption factor (100%) / body weight (70 kg adult).
e Short-term Inhalation MOE = NOAEL (9.0 mg/kg/day for short-term exposure) / Inhalation Dose (mg/kg/day). Level of concern = 100.
f Intermediate-term Inhalation MOE = NOAEL (7.3 mg/kg/day for intermediate-term exposure) / Inhalation Dose (mg/kg/day). Level of concern = 100.
* in the case where there are several crops under the crop group assessed, the crop with the highest amount of seeds planted per day was assessed to cover that crop group (i.e., beans and peas, cereal grains)

9.3 Post-Application Exposure

HED uses the term "post-application" to describe those individuals who can be exposed to pesticides after entering areas previously treated with pesticides and performing certain tasks or activities (also often referred to as reentry exposure). Post-application exposures are expected to occur primarily via the dermal route. Based on the Agency's current practices, a quantitative occupational post-application inhalation exposure assessment was not performed for fluxapyroxad at this time; an inhalation exposure assessment was performed for occupational handlers. This assessment resulted in risk estimates that did not exceed HED's level of concern at baseline inhalation PPE. Handler exposure resulting from application of pesticides outdoors is likely to result in higher exposure than post-application exposure. Therefore, it is expected that these handler inhalation exposure estimates would be protective of most occupational post-application inhalation exposure scenarios. However, there are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and re-suspension of dusts and/or particulates that contain pesticides. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009. The Agency received the SAP's final report on March 2, 2010 (http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html). The Agency is in the process of evaluating the SAP report as well as available post-application inhalation exposure data generated by the Agricultural Reentry Task Force and may, as appropriate, develop policies and procedures, to identify the need for and, subsequently, the way to incorporate occupational post-application inhalation exposure into the Agency's risk assessments. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative occupational post-application inhalation exposure assessment for fluxapyroxad.

The potential for post-application exposures following the planting of fluxapyroxad-treated seeds is unlikely because sustained levels of contact with treated seed after it has been placed in the soil or other planting media would not be expected because no routine cultural practice required for the production of agricultural commodities involves such an activity as defined in the no/low contact criteria in the Worker Protection Standard (WPS). Therefore, no quantitative post-application assessment is required for exposure to treated seeds that have already been planted.

10.0 REFERENCES

Fluxapyroxad; Occupational Exposure Assessment to Support the Request for Registration of Fluxapyroxad on seed and various food crops, J. Miller D390242, 2/8/12

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Fluxapyroxad (BAS 700F). Report of the Residues of Concern Knowledgebase Subcommittee (ROCKS). I. Negrón-Encarnación, D390225, 7/14/11

Fluxapyroxad (BAS 700F) New Chemical Screen for Toxicology. J. Ryman, D377679, 7/30/10

CARC Report (J. Kidwell, June 9, 2011, TXR 0055930).

APPENDIX A. TOXICOLOGY PROFILE AND EXECUTIVE SUMMARIES

A.1 TOXICOLOGY DATA REQUIREMENTS

The requirements (40 CFR 158.340) for food use for fluxapyroxad are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Guideline No.	Study Type	Technical		MRID No.
		Required	Submitted	
870.3100	Subchronic (Oral) Toxicity - Rodent	Y	Y	47923567 47923568
870.3150	Subchronic (Oral) Toxicity - Non-Rodent	Y	Y	47923569
870.3200	21/28-Day Dermal Toxicity	N	Y	47923571
870.3250	90-Day Dermal Toxicity	N	N	---
870.3465	90-Day Inhalation Toxicity	Y	N	---
870.3700a	Prenatal Developmental Toxicity - Rodent	Y	Y	47923603
870.3700b	Prenatal Developmental Toxicity - Non-Rodent	Y	Y	47923604
870.3800	Reproduction and Fertility Effects	Y	Y	47923602
870.4100a	Chronic (Oral) Toxicity - Rodent	Y	Y	47923591 47923592
870.4100b	Chronic (Oral) Toxicity - Non-Rodent (Dog)	Y	Y	47923570
870.4200a	Carcinogenicity - Rat	Y	Y	47923591
870.4200b	Carcinogenicity - Mouse	Y	Y	47923592
870.4300	Combined Chronic Toxicity /Carcinogenicity	Y	Y	47923591 47923592
870.6100a	Neurotoxicity - Acute Delayed Neurotox.- Hen	N	N	---
870.6100b	Neurotoxicity - Subchronic - Hen	N	N	---
870.6200a	Neurotoxicity Screening Battery - Acute - Rat	Y	Y	47923605
870.6200b	Neurotoxicity Screening Battery -Subchronic - Rat	Y	Y	47923606
870.6300	Developmental Neurotoxicity……	N	N	---
870.7800	Immunotoxicity……..	Y	Y	47923633

A.2 TOXICITY PROFILES

A.2.1 Acute Toxicity

Table A.2.1.1 Acute Toxicity Profile – Fluxapyroxad				
Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral – rat (females)	47923607	LD_{50} = >2000 mg/kg	III
870.1200	Acute dermal – rat	47923559	LD_{50} >2000 mg/kgM & F	III
870.1300	Acute inhalation – rat	47923560	LC_{50} >5.1 mg/L M & F	IV
870.2400	Acute eye irritation – rabbit	47923562	Slightly irritating	IV
870.2500	Acute dermal irritation – rabbit	47923561	Slightly irritating	IV
870.2600	Dermal sensitization – guinea pig	47923813	No sensitization	-

TableA.2.1.2 Acute Toxicity Profile – Fluxapyroxad Metabolites				
Guideline No.	**Study Type**	**MRID(s)**	**Results**	**Toxicity Category**
870.1100	Acute oral – rat (females) **M-1**	47701678	LD_{50} = >2000 mg/kg	III
870.1100	Acute oral – rat (females) **M-3**	47701679	LD_{50} = >2000 mg/kg	III
870.1100	Acute oral – rat (females) **M-25**	47701680	LD_{50} = >2000 mg/kg	III
870.1100	Acute oral – rat (females) **M-28**	47701755	LD_{50} = >2000 mg/kg	III
870.1100	Acute oral – rat (females) **I-3**	47701681	LD_{50} = >2000 mg/kg	III
870.1100	Acute oral – rat (females) **I-4**	47701682	LD_{50} = >2000 mg/kg	III
870.1100	Acute oral – rat (females) **I-5**	47701683	LD_{50} = >2000 mg/kg	III

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile Toxicity Profile for Fluxapyroxad (BAS 700F)		
Guideline No Study Type	**MRID/Classification Doses**	**Results**
870.3050 28 day dietary in rats	47923564 (2009) Acceptable, guideline 0, 100, 500, 2000, 6000 ppm 0/0, 9/9.4, 43.7/47.8, 176/183, 530/531, mkd M/F	**Males** NOAEL=100 ppm (9.0 mkd) LOAEL 500 ppm (176 mkd) based on thyroid follicular hypertrophy/hyperplasia and clinical chemistry changes **Females** NOAEL=500 ppm (47.8 mkd) LOAEL=2000 ppm (531 mkd) based on decreased prothrombin time and clinical chemistry changes
Non-Guideline Thyroid hormone levels-28 days-rat	47923594 (2009) Acceptable, non-guideline 0, 50, 250, 1500, 3000 ppm (0/0, 3.5/4.4, 19/20, 105/117, 214/237 mkd)	Increased TSH, decreased T4 in males only at 3000 ppm only days 14 through 28. Accompanied by increased absolute and relative liver and thyroid weights. Supports hypothesis that an increased conjugation and elimination of circulating thyroxine (T_4) leads to compensatory release of thyroid stimulating hormone (TSH) from the pituitary, secondary to BAS 700 F liver enzyme induction.
Non-Guideline Perchlorate discharge study-28 days rat	47923595 (2009) Acceptable, non-guideline 0, 3000 ppm	The similarities in the behavior of BAS 700 F to phenobarbitol in this perchlorate discharge assay support the hypothesis that BAS 700 F causes increases in thyroid hormones by an indirect mechanism.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile Toxicity Profile for Fluxapyroxad (BAS 700F)		
Guideline No Study Type	**MRID/Classification Doses**	**Results**
	0/0, 283/247 mkd	
Non-Guideline Enzyme induction	47923599 (20210) Acceptable, non-guideline 50 ppm	Mechanistic investigations of enzyme induction (thyroid and liver).
Non-Guideline Enzyme induction	47923593 (2010) Acceptable, non-guideline 0, 250, 1500, 3000 ppm 0/0, 16/19, 96/126, 192/234 mkd	Mechanistic investigations of enzyme induction (thyroid and liver).
Non-Guideline S-phase induction 1-3-7-14 days	47923598 (2010) Acceptable, non-guideline 0, 50, 250, 1500, 3000 ppm	Mechanistic tnvestigations of hepatocellular proliferation.
Non-Guideline S-phase induction 7-28-91 days	47923597 (2010) Acceptable, non-guideline 50 ppm only	Mechanistic tnvestigations of hepatocellular proliferation.
870.3050 28 day dietary in mice	47923565 (2009) Acceptable, guideline 0, 500, 2500, 7000 ppm 0/0, 112/150, 552/746, 1452/2100 mkd M/F	**Males** NOAEL=2500 ppm (552 mkd) LOAEL =7000 ppm (1452 mkd) based on hematological changes. **Females** NOAEL=7000 ppm (2100 mkd) LOAEL=Not observed
No EPA guideline, OECD 407 –28 day dietary in dogs	47923566 (2009) Acceptable/non-EPA guideline 0, 2500, 7500, 20000 ppm 0/0, 74/85, 211/230, 521/503 mkd M/F	NOAEL=2500 ppm (74/85 mkd M/F) LOAEL-=7500 ppm (211/230 mkd M/F) based on vomiting (M/F) and clinical chemistry changes
870.3100 90-day dietary in mice	47923568 (2009) Acceptable/guideline 0, 100, 400, 2000, 6000 ppm 0/0, 21/32, 77/128, 390/610, and	**Males** NOAEL=2000 ppm (390 mkd) LOAEL 6000 ppm (1136 mkd) based on decreased body weight and body weight gain and multifocal necrosis in the liver **Females** NOAEL=6000 ppm (1657 mkd)

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile Toxicity Profile for Fluxapyroxad (BAS 700F)		
Guideline No Study Type	**MRID/Classification Doses**	**Results**
	1136/1657 mkd (M/F)	LOAEL=Not observed.
870.3100 90-Day dietary in rats	47923567 (2009) Acceptable, guideline 0, 100, 500, 2000, 6000 ppm 0/0, 6.1/7.3, 31.2/35.1, 126/144, and 407/424 mkd (M/F)	NOAEL = 500 ppm (31.2 mkd) males; 100 ppm (7.3 mkd) females LOAEL = 2000 ppm (126 mkd) males; 500 ppm (35.1 mkd females) based on changes in thyroid hormone levels and thyroid follicular hypertrophy/hyperplasia
870.3150 90-Day Oral Toxicity Feeding-dog	47923569 (2009) Acceptable/guideline 0, 300, 1500, 10000/7500 (M/F) 0/0, 9/10, 45/51, 295/238 mkd M/F	NOAEL=1500 ppm (45/51 mkd M/F) LOAEL=10000 ppm (295 mkd) males, 7500 ppm (238 mkd) females based on vomiting and clinical chemistry changes
870.3200 28-Day Dermal Toxicity-rat	47923571 (2009) Acceptable, guideline 0, 100, 300, 1000 mkd	NOAEL=1000 mkd LOAEL=not observed
870.3465 90-Day Inhalation		Still required, data gap
870.3700a Prenatal Developmental- rat	47923603 (2009) Acceptable, guideline 0, 25, 200 and 1000 mkd (gavage in CMC)	**Maternal** NOAEL=200 mkd LOAEL =1000 mkd based on increased absolute and relative thyroid weights and thyroid hypertrophy/hyperplasia **Offspring** NOAEL=1000 mkd LOAEL =Not observed
870.3700b Prenatal Developmental-rabbit	47923604 (2009) Acceptable, guideline 0, 10, 25 and 60 mkd	**Maternal** NOAEL=25 mkd LOAEL =60 mkd based on decreased body weight **Offspring** NOAEL=25 mkd LOAEL =60 mkd based on decreased fetal body weights and increased incidence of paw hyperflexion
870.3800 Reproduction and Fertility Effects-rat	47923602 (2009) Acceptable, guideline 0, 10, 50 and 300 mkd	**Parental** NOAEL=10 mkd LOAEL =50 mkd based on thyroid follicular hypertrophy/hyperplasia **Fertility/Reproductive Performance** NOAEL=300 mkd LOAEL =Not observed. **Offspring**

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile Toxicity Profile for Fluxapyroxad (BAS 700F)		
Guideline No Study Type	**MRID/Classification Doses**	**Results**
		NOAEL=10 mkd LOAEL =50 mkd decreased pup body weight/body weight development
870.4100 Chronic Toxicity-dog	47923570 (2009) Acceptable/guideline 0, 300, 1500, 12000/9000 ppm (M/F) 0/0, 8/9, 39/43, 335/257 mkd M/F	**Females** NOAEL=300 ppm (9 mkd) LOAEL =1500 ppm (43 mkd) based on hepatic fibrosis and clinical chemistry changes **Males** NOAEL=1500 ppm (39mkd) LOAEL=12000 ppm (335 mkd) based on vomiting, heptaic fibrosis and cirrhosis, and clinical chemistry changes (liver enzyme elevation)
870.4300 Chronic toxicity/carcinogenicity in rats	47923591 (2009) Acceptable, guideline 0, 50, 250, 1500, 3000 ppm 0/0, 2.1/2.7, 11/14, 68/82, 145/182 mkd (M/F)	**Chronic toxicity** NOAEL=50 ppm (2.1/2.7 mkd in males/females) LOAEL =250 ppm (11/1 mkd) based on neoplastic changes in the liver (foci, masses). **Carcinogenicity-see CARC report** Classified as" not likely to be carcinogenic to humans" at doses below those that cause liver enzyme induction in rats.
870.4300 Chronic toxicity/carcinogenicity in mice	47923592 (2009) Acceptable, guideline 0, 150, 750, 3000, 6000 ppm 0/0, 21/33, 107/158, 468/652, 996/1307 mkd (M/F)	**Chronic toxicity** NOAEL=750ppm (158/107 mkd M/F) LOAEL =3000 ppm (468/652) mkd M/F based on decrease body weight. **Carcinogenicity** NOAEL=6000 ppm (996/1307 mkd M/F) LOAEL =Not observed
Gene Mutation 870.5100 *In vitro* Bacterial Gene Mutation	47923572 (2008) Acceptable, guideline 0, 20, 100, 500, 2500, 5000 µg/plate ±S9	Not mutagenic in the reverse mutation assay in *Salmonella typhimurium* or *Escherichia coli* with or without metabolic activation.
Gene Mutation 870.5300 *In vitro* Mammalian Cells Gene Mutation (Chinese Hamster Ovary Cells)	47923579 (2007) Acceptable, guideline 0-100 µg/ml ±S9	Does not induce forward mutations in CHO cells with or without metabolic activation.
Cytogenetics 870.5375 *In vitro* Mammalian Cytogenetics Chromosomal Aberration Assay-human peripheral blood lymphocytes	47923577 (2008) Acceptable, guideline 0-400 µg/ml ±S9	Does not cause clastogenic effects in V79 cells with or without metabolic activation.
Cytogenetics-other	47923584 (2006)	Did not lead to any increase in polychromatic erythrocytes.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile Toxicity Profile for Fluxapyroxad (BAS 700F)		
Guideline No Study Type	**MRID/Classification Doses**	**Results**
870.5395 *In Vivo* Mammalian Cytogenetics - Erythrocyte Micronucleus-mouse	Acceptable, guideline 0, 500, 1000, 2000 mkd	
870.6200a Acute Neurotoxicity-rat	47923605 (2009) Acceptable, guideline 0, 125, 500, 2000 mkd	NOAEL (neurotoxicity) =125 mk LOAEL (neurotoxicity)=500 mk based on decreased motor activity (both sexes) and decreased rearing (males only).
870.6200b Subchronic Neurotoxicity-rat	47923606 (2009) Acceptable, guideline 0, 200, 100, and 5000 ppm 0, 11.5/13.4, 57.7/67.2, 302.2/337.7 mkd M/F	NOAEL (neurotoxicity)=5000 ppm (302/338 mkd M/F) LOAEL (neurotoxicity) =Not observed
870.7485 Metabolism and Pharmacokinetics-rat	47923555 (2009) 47923556 (2009)	The times to maximum plasma levels (T_{MAX}) were 24 hours (500 mg/kg bw), 8 hours (50 mg/kg bw), and 1 hour (5 mg/kg bw) in both sexes. No sex differences in the rate or extent of absorption was observed. AUCs scaled with dose, indicating that absorption was not saturated. Radioactivity was widely distributed in both sexes with a similar pattern: the highest concentrations were found in the gut contents and stomach contents. However, lower concentrations were found in numerous other organs/tissues, including the liver, thyroid, adrenal glands, kidney, pancreas, testes/uterus, and brain. For males and females, radioactivity declined in all tissues over time. The time course of the amount of radioactivity found in urine and feces indicated the excretion occurred predominantly within three days after dosing. Bile duct cannulation experiments showed that the bile was a major route of excretion. The main biotransformation steps of BAS 700 F in rats are hydroxylation at the biphenyl ring system, N-demethylation at the pyrazole ring system, loss of a fluorine atom at the biphenyl ring system, and conjugation with glucuronic acid or with glutathione derivatives. A further, but negligible transformation route is cleavage at the amide bond between the pyrazole ring system and the biphenyl ring system.
870.7600 Dermal penetration	47923632 (2010) Acceptable, guideline 5.6, 33,4, 1670 µg/cm^2 for 8 h exposure and 24 and 120 h termination	The dermal absorption factor is 8.38%.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile Toxicity Profile for Fluxapyroxad (BAS 700F)		
Guideline No Study Type	**MRID/Classification Doses**	**Results**
	*In a formulation with pyraclostrobin (BAS 500 F)	
870.7800 Immunotoxicity-mice (male)	47923633 (2009) Acceptable, guideline 0, 500, 2000 and 6000 ppm 0, 106, 450 and 1323 mg/kg/d	Not immunotoxic.
Non-guideline S-phase Response Liver 1, 3, 7, 14 days-rat	47923598 (2009) 0, 50, 250, 1500 and 3000 ppm	Cell proliferation in both sexes was dose-dependent at maximal at Day 7 (males) and Days 7& 14 (females).
Non-guideline S-phase Response Liver 7, 28, 91 days-rat	47923596 (2009) 0, 50 ppm (nominal)-Acceptable, non-guideline 47923596 (2009) Acceptable, non-guideline 0. 250, 1500, 3000 ppm (nominal)	Cell proliferation in males was maximal at Day 7 and was nearly absent by Day 28. Cell proliferation in females was maximal at Day 7 declined Days 28 and 91, but was still above controls in higher dose groups. All effects were dose-dependent. Reversibility investigated at 28 days treat/28 days recovery.
Non-guideline Enzyme induction (Phase I and Phase II) with Thyroid Hormone Levels-14 days	47923593 (2009) Acceptable, non-guideline 0, 250, 1500, 3000 ppm 1/1, 16/19, 96/126, 192/234 mkd	Dose-dependent increase in Phase I and Phase II enzymes in both sexes and increased liver and thyroid weights with correlating histopathology. Effects partially (thyroid histopathology) to totally (all other effects) reversible in 4 week recovery group.
Non-OPPTS guideline, OECD 486	47923589 (2009) Acceptable, non-guideline 0, 1000, 2000 mkd	Does not induce unscheduled DNA synthesis.

Table A.2.5 Subchronic, Chronic and Other Toxicity Profile Toxicity Profile for Metabolite M700F001		
Guideline No Study Type	**MRID Classification Doses**	**Results**
870.3100 90-Day dietary in rats	47923608 (2009) Acceptable, -guideline 0/0, 94.6/98.8,	NOAEL=953.6/983.1 mkd in M/F LOAEL=Not observed

Table A.2.5 Subchronic, Chronic and Other Toxicity Profile Toxicity Profile for Metabolite M700F001		
Guideline No Study Type	**MRID Classification Doses**	**Results**
	285.7/295.1, 953.6/983.1 mkd M/F	
870.3700b Prenatal Developmental-rabbit	47923613 (2009) Acceptable, guideline 0, 40, 100, and 250 mkd	**Maternal** NOAEL=250 mkd LOAEL =Not observed. **Offspring** NOAEL=250 mkd LOAEL =Not observed
Gene Mutation 870.5100 *In vitro* Bacterial Gene Mutation	47923609 (2009) Acceptable, guideline	Not mutagenic.
Gene Mutation 870.5300 *In vitro* Mammalian Cells Gene Mutation (Chinese Hamster Ovary Cells)	47923611 (2009) Acceptable, guideline	Not mutagenic.
Cytogenetics 870.5375 *In vitro* Mammalian Cytogenetics Chromosomal Aberration Assay-human peripheral blood lymphocytes	47923610 (2009) Acceptable, guideline	Not clastogenic.
Cytogenetics-other 870.5395 *In Vivo* Mammalian Cytogenetics - Erythrocyte Micronucleus-mouse	47923612 (2009) Acceptable, guideline O, 500, 1000, 2000 mkd	Did not lead to any increase in polychromatic erythrocytes.

Table A.2.5 Subchronic, Chronic and Other Toxicity Profile Toxicity Profile for Metabolite M700F002		
Guideline No Study Type	**MRID Classification Doses**	**Results**
870.3050 28 day dietary in rats	47923615 (2009) Acceptable, guideline 0/0, 113/113.4, 275.9/394.8, 1164.8/1253.3 mkd	NOAEL= 1164.8/1253.3mkd in M/F LOAEL=Not observed
870.3100	47923616 (2009)	

Table A.2.5 Subchronic, Chronic and Other Toxicity Profile Toxicity Profile for Metabolite M700F002		
Guideline No Study Type	**MRID Classification Doses**	**Results**
90-Day dietary in rats	Acceptable, -guideline 0/0, 113/113.4, 275.9/394.8, 1164.8/1253.3 mkd 0/0, 95.1/98.0, 285.3/299.5, 958.4/928.7 mkd M/F	NOAEL=958.4/928.7 mkg M/F LOAEL=not observed
870.3700b Prenatal Developmental-rabbit	47923622 (2000) Acceptable, -guideline 0, 100, 300, 1000 mkd	**Maternal** NOAEL=300 mkd LOAEL =1000 mkd based on increased mortality and abortions. **Offspring** NOAEL=1000 mkd LOAEL =Not observed
Gene Mutation 870.5100 *In vitro* Bacterial Gene Mutation	47923617 (2007) Acceptable, guideline	Not mutagenic.
Gene Mutation 870.5300 *In vitro* Mammalian Cells Gene Mutation (Chinese Hamster Ovary Cells)	47923619 (2008) Acceptable, -guideline	Not mutagenic.
Cytogenetics 870.5375 *In vitro* Mammalian Cytogenetics Chromosomal Aberration Assay-human peripheral blood lymphocytes	47923618 (2008) Acceptable, -guideline	Not clastogenic.
Cytogenetics-other 870.5395 *In Vivo* Mammalian Cytogenetics - Erythrocyte Micronucleus-mouse	47923620 (2009) Acceptable, guideline O, 375, 750, 1500 mkd	Did not lead to any increase in polychromatic erythrocytes.
Non-OPPTS guideline, OECD 417	47923621 (2009) Acceptable, non-guideline 1000 mkd, oral (gavage)	M700F002 is systemically bioavailable and its presence in the bone marrow and blood after an oral application is confirmed.

Table A.2.4 Subchronic, Chronic and Other Toxicity Profile Toxicity Profile for Metabolite M700F048		
Guideline No Study Type	**MRID Classification Doses**	**Results**
870.3050 28 day dietary in rats	47923624 (2009) Acceptable, guideline\ 0, 50, 200, 1000 mkd (nominal) 0/0, 47.l/51.4, 189.3/208.2, not calculable/1477.8 M/F	NOAEL=47.1/51.4 mkd in males, 1477.8 mkd females. LOAEL= 189.3 in mkd males based on decreased absolute and realtive monocyte counts. The LOAEL was not observed in females.
870.3700b Prenatal Developmental-rabbit	47923631 (2009) Acceptable, guideline 0, 10, 30 and 100 mg/kg bw/d	**Maternal** NOAEL=30 mkd LOAEL = 100 mkd based on mortality, abortions, and resorptions **Offspring** NOAEL=30 mkd LOAEL =100 mkd based on incresed aborptions and late resorptions.
Gene Mutation 870.5100 *In vitro* Bacterial Gene Mutation	47923625 (2009) Acceptable, guideline	Not mutagenic.
Gene Mutation 870.5300 *In vitro* Mammalian Cells Gene Mutation (Chinese Hamster Ovary Cells)	47923627 (2009) Acceptable, guideline	Not mutagenic.
Cytogenetics 870.5375 *In vitro* Mammalian Cytogenetics Chromosomal Aberration Assay-human peripheral blood lymphocytes	47923626 (2009) Acceptable, guideline	Clastogenic with metabolic activation.
Cytogenetics-other 870.5395 *In Vivo* Mammalian Cytogenetics - Erythrocyte Micronucleus-mouse	47923628 (2009) Acceptable, guideline 0, 500, 1000, 2000 mkd	Did not lead to any increase in polychromatic erythrocytes.
870.7485 Metabolism and Pharmacokinetics-rat	47923557 (2009) Acceptable, guideline	In both sexes, the major route of excretion was the feces (85.47% in males and 86.4% in females) with maximum excretion within 12-24 hours after dosing. The minor route of excretion was in the urine (2.4% in males and 6.8% in females).
Non-OPPTS guideline,	47923630 (2009)	M700F048 is 5077265 is systemically bioavailable and its

Table A.2.4 Subchronic, Chronic and Other Toxicity Profile Toxicity Profile for Metabolite M700F048		
Guideline No Study Type	**MRID Classification Doses**	**Results**
OECD 417	Acceptable, non-guideline 1000 mkd, oral (gavage)	presence in the bone marrow, blood and liver after an oral application is confirmed.
Non-OPPTS guideline, OECD 486	47923629 (2009) Acceptable, non-guideline 0, 1000, 2000 mkd	Does not induce unscheduled DNA synthesis.

Table A.2.5 Subchronic, Chronic and Other Toxicity Profile Toxicity Profile for Artificial Batch		
Guideline No Study Type	**MRID Classification Doses**	**Results**
Gene Mutation 870.5100 *In vitro* Bacterial Gene Mutation	47923573 (2009) Acceptable, guideline	No evidence of mutagenicity.
Gene Mutation 870.5300 *In vitro* Mammalian Cells Gene Mutation (Chinese Hamster Ovary Cells)	47923580 (2009) Acceptable, guideline	No evidence of forward mutations.
Cytogenetics 870.5375 *In vitro* Mammalian Cytogenetics Chromosomal Aberration Assay-human peripheral blood lymphocytes	47923578 (2009) Acceptable, guideline	Clastogenic in V79 cells in the presence or absence of metabolic activation.
Cytogenetics-other 870.5395 *In Vivo* Mammalian Cytogenetics - Erythrocyte Micronucleus-mouse	47023585 (2009) Acceptable, guideline 0, 500, 1000, 2000 mkd	Did not lead to any increase in polychromatic erythrocytes
Non-OPPTS guideline, OECD 486	47923590 (2009) Acceptable, non-guideline 0, 2.5, 5 mkd	Does not induce unscheduled DNA synthesis.

Table A.2.5 Subchronic, Chronic and Other Toxicity Profile Toxicity Profile for Impurity B		
Guideline No Study Type	**MRID Classification Doses**	**Results**
Gene Mutation 870.5100 *In vitro* Bacterial Gene Mutation	47923574 (2009) Acceptable, guideline	Not mutagenic.
Gene Mutation 870.5300 *In vitro* Mammalian Cells Gene Mutation (Chinese Hamster Ovary Cells)	47923581 (2009) Acceptable, guideline	Not mutagenic.
Cytogenetics-other 870.5395 *In Vivo* Mammalian Cytogenetics - Erythrocyte Micronucleus-mouse	47923586 (2009) Acceptable, guideline 0, 15, 30, 60 mkd	Did not lead to any increase in polychromatic erythrocytes.

Table A.2.3 Subchronic, Chronic and Other Toxicity Profile Toxicity Profile for Impurity C		
Guideline No Study Type	**MRID Classification Doses**	**Results**
Gene Mutation 870.5100 *In vitro* Bacterial Gene Mutation	47923576 (2008) Acceptable, guideline	Not mutagenic.
Gene Mutation 870.5300 *In vitro* Mammalian Cells Gene Mutation (Chinese Hamster Ovary Cells)	47923583 (2008) Acceptable, guideline	Not mutagenic.
Cytogenetics-other 870.5395 *In Vivo* Mammalian Cytogenetics - Erythrocyte Micronucleus-mouse	47923588 (2008) Acceptable, guideline 0, 500, 1000, 2000 mkd	Did not lead to any increase in polychromatic erythrocytes.

A.3 HAZARD IDENTIFICATION AND ENDPOINT SELECTION

A.3.1 Acute Reference Dose (aRfD) – All populations (General Population, including infants and children and females ages 13-49)

Study Selected: Acute Neurotoxicity Study in Rats

MRID No.: 47923606

Dose and Endpoint for Risk Assessment: NOAEL= 125 mg/kg/day. The LOAEL of 500 mg/kg/day was based on decreased motor activity (both sexes) and decreased rearing (males only) seen on the day of dosing.

Uncertainty Factor: 100x (10x interspecies extrapolation, 10x intraspecies variability); FQPA SF = 1X

$$\textbf{Acute RfD= acute PAD} = \frac{125 \text{ mg/kg/day}}{100} = \textbf{1.25 mg/kg/day}$$

Comments about Study/Endpoint/Uncertainty Factors: The study is appropriate for acute dietary exposure due to the route (oral) and duration (acute) of dosing. The effects are clearly adverse and result from a single exposure.

Endpoints from the developmental rat and rabbit studies as well as the 2-generation reproduction study were not selected since there were no effects seen that were attributable to a single exposure. Therefore, the dose and endpoint from the ACN study was selected and is considered protective of potential acute toxicity for all populations (i.e. the general population, including infants and children and females ages 13 to 49 years old).

A.3.2 Chronic Reference Dose (cRfD)-All Populations

Study Selected: Chronic Toxicity/Carcinogenicity Study in Rats

MRID No: 47923591

Dose and Endpoint for Risk Assessment: NOAEL= 2.1 mg/kg/day (50 ppm). The LOAEL of 11 mg/kg/day (250 ppm) was based on non-neoplastic changes (increased liver weight, liver foci, changes in clinical chemistry, including prothrombin time and cholesterol levels) in the liver of male rats.

Uncertainty Factor: 100x (10x interspecies extrapolation, 10x intraspecies variability); FQPA SF = 1X

Chronic RfD = chronic PAD= 2.1 mg/kg/day = **0.021 mg/kg/day**
100

Comments about Study/Endpoint/Uncertainty Factors: The study is appropriate for chronic dietary exposure due to the route (oral) and duration (chronic) of dosing. These effects are consistent with the liver being the target organ and are supported by the effects seen in the 28- and 90-day studies. This point of departure is also protective of the liver adenomas occurring at 250 ppm in male rats.

A.3.3 Incidental Oral Exposure (Short-Term (1-30 days))

Study Selected: 28-Day Dietary Toxicity Study in the Rat

MRID No: 47923564

Dose and Endpoint for Risk Assessment: NOAEL = 9 mg/kg/day (100 ppm) in males. The LOAEL in males of 176 mg/kg/day (500 ppm) was based on changes in thyroid follicular hypertrophy/hyperplasia.

Uncertainty Factor: The residential level of concern for MOE is 100 (10X inter-species, 10X intra-species factor) (proposed)

Comments about Study/Endpoint/UF: The selected endpoint is the most sensitive endpoint and most sensitive species for this route and duration of expsoure.

A.3.4 Incidental Oral Exposure (Intermediate-Term (1-6 months))

Study Selected: 90-Day Dietary Toxicity Study in the Rat

MRID No: 47923567

Dose and Endpoint for Risk Assessment: NOAEL = 7.3 mg/kg/day (100 ppm). The LOAEL = 500 ppm (35.1 mg/kg/day) based on thyroid hormones and thyroid follicular hypertrophy/hyperplasia.

Uncertainty Factor: The residential level of concern for MOE is 100.

Comments about Study/Endpoint/UF: The selected endpoint is the most sensitive endpoint and most sensitive species for this route and duration of expsoure.

A.3.5 Occupational and Residential Dermal Exposure (Short- and Intermediate-Term)

In a 28-day dermal toxicity study in rats, no dermal irritation or systemic effects were observed up to the limit dose of 1000 mg/kg/day. This is a route-specific study that also assessed all of the endpoints used in the other exposure scenarios and durations of exposure (e.g. neurological endpoints, thyroid and liver histopathology). In addition, no increased susceptibility was seen

between offspring and adult animals in the developmental toxicity studies in rats and rabbits and in the 2-generation reproduction study in rats. **Therefore, the quantification of dermal risk is not required since no hazard was identified.**

A.3.6 Occupational and Residential Inhalation Exposure (Short-Term)

Study Selected: 28-Day Dietary Toxicity Study in the Rat

MRID No: 47923564

Dose and Endpoint for Risk Assessment: NOAEL = 9 mg/kg/day (100 ppm) in males. The LOAEL in males of 176 mg/kg/day (500 ppm) was based on changes in thyroid hormones and thyroid follicular hypertrophy/hyperplasia.

Uncertainty Factor: The occupational and residential level of concern for MOE is 100.

Comments about Study/Endpoint/UF: No inhalation studies are available for fluxapyroxad; therefore, a 28-day oral toxicity study in rats was used for inhalation risk assessment. The selected endpoint is the most sensitive endpoint and most sensitive species for this duration of exposure.

A.3.7 Occupational and Residential Inhalation Exposure (Intermediate-Term)

Study Selected: 90-Day Dietary Toxicity Study in the Rat

MRID No: 47923567

Dose and Endpoint for Risk Assessment: NOAEL = 7.3 mg/kg/day (100 ppm). The LOAEL = 500 ppm (35.1 mg/kg/day) based on thyroid follicular hypertrophy/hyperplasia.

Uncertainty Factor: The occupational and residential level of concern for MOE is 100.

Comments about Study/Endpoint/UF: No inhalation studies are available for fluxapyroxad; therefore, a 90-day oral toxicity study in rats was used for inhalation risk assessment. The selected endpoint is the most sensitive endpoint and most sensitive species for this route and duration of expsoure.

Based on the proposed use pattern for fluxapyroxad, occupational long-term inhalation exposure is not anticipated.

A. 4 EXECUTIVE SUMMARIES

A.4.1 Subchronic Toxicity

870.3100 90-Day Oral Toxicity – Rat MRID 47923567

BAS 700 F (Batch: COD–000826; Purity: 99.6%) was administered to male and female Wistar rats at dietary dose levels of 0, 100, 500, 2000, or 6000 ppm (0/0, 6.1/7.3, 31.2/35.1, 126/144, and 407/424 mg/kg bw/day in males/females) for at least 90 days. Significant decreases in body weight and body weight gain were observed in 6000 ppm males and females and were considered adverse.

A functional observational battery and motor activity measurements were performed at the end of the dietary exposure period. However, no evidence of neurotoxicity was observed in these investigations. Also, no signs of neurotoxicity were noted in daily cageside or weekly clinical examinations and no opthamoscopic changes were noted.

In the liver, a number of changes were observed. These included changes of a number of clinical chemistry parameters, increased absolute and relative liver weights at ≥ 500 ppm as well as histopathological changes (increased incidence and severity of centrilobular hepatocyte hypertrophy in both sexes at ≥ 500 ppm (which is considered adaptive and not adverse), and hepatocellular single cell necrosis in top dose males (which is considered clearly adverse). The clinical chemistry changes considered potentially indicative of adverse effects were increased serum cholesterol and triglycerides in females at ≥ 2000 ppm and in males at 6000 ppm and decreased prothrombin time in females at ≥ 500 ppm, which indicated potential for increased blood clotting. The increase of γ-glutamyltransferase activities in males at ≥2000 ppm and the top dose group of both sexes was regarded equivocal, since elevated GGT can be associated with both adaptive and adverse effects

Changes in thyroid hormone levels were observed in males at ≥100 ppm with thyroid follicular cell hypertrophy/hyperplasia present at ≥2000 ppm. In females, both changes in thyroid hormone levels and thyroid follicular hypertrophy/hyperplasia were observed at ≥500 ppm.

Additionally, an increased tubular deposition of pigment indicative of a mild tubulonephrosis was observed in kidneys of top dose females and was not considered adverse.

The LOAEL is 2000 ppm (126 mg/kg bw/day) in males and 500 ppm (35.1 mg/kg bw/day) in females, based on thyroid follicular hypertrophy and hyperplasia. The NOAEL is 500 ppm (31.2 mg/kg bw/day) in males and 100 ppm (7.3 mg/kg bw/day) in females.

This study is classified as **totally reliable** (**acceptable/guideline)** and satisfies the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3100; OECD 408) in rats.

870.3100 90-Day Oral Toxicity – Mice MRID 47923568

BAS 700 F (Batch: COD–000826; Purity 99.6%) was administered to C57BL/6 J Rj mice (10/sex/dose) at dietary dose levels of 0, 100, 400, 2000 and 6000 ppm (corresponding to 0/0, 21/32, 77/128, 390/610, and 1136/1657 mg/kg bw/day) for at least 91 days. Significant decreases in body weight (-12.6%) and body weight gain (-32.5%) were observed in top dose males were considered adverse.

The liver was identified as a target organ as indicated by changes of a number of clinical chemistry parameters down to a dietary dose level of 400 ppm in males as well as statistically significant increases of absolute and relative liver weights at 2000 ppm or higher in both sexes. The clinical chemistry changes consisted of increased alkaline phosphatase, alanine-aminotransferase (ALAT) and urea levels in top dose males as well as decreased triglyceride (males only) and albumin, total protein and cholesterol levels in both sexes. An increased incidence of multifocal necrosis was observed in the liver of 5/10 6000 pm males and, in conjunction with increased liver enzymes, was considered potentially adverse.

The LOAEL is 6000 ppm (1136 mg/kg bw/day) in males, based on decreased body weight and body weight gain and multifocal necrosis in the liver. The LOAEL in females was not observed. The NOAEL is 2000 ppm (390 mg/kg bw/day) in males and 6000 ppm (1657 mg/kg bw/day) in females.

This 90-day oral toxicity study in the mouse is classified as **totally reliable (acceptable/guideline)** and satisfies guideline requirements for a 90-day oral toxicity study (OPPTS 870.3100; OECD 408) in mice.

870.3150 90-Day Oral Toxicity – Dog MRID 47923569

Administration of BAS 700 F (Batch: COD – 000899; Purity: 99.7%) to groups of 5 Beagle dogs/sex/dose at dietary dose levels of 0, 300, 1500 and 10000 ppm in males (0, 9, 45, and 295 mg/kg bw/day) and 0, 300, 1500 and 7500 ppm in females (0, 10, 51, and 238 mg/kg bw/day) for at least 90 days resulted in impaired food consumption in each two high dose males and females. This was accompanied by decreased body weight development in one high dose female only. Furthermore, vomiting was recorded in all male and female dogs of the high dose group during the first two days of treatment.

The liver was identified as the major target organ as indicated by changes in a number of clinical chemistry parameters at 1500 and/or 10000/7500 ppm as well as statistically significant changes of absolute and/or relative liver weights at 10000 ppm in males and 7500 ppm in females. The clinical chemistry changes considered potentially adverse were increase ALP and GGT in both sexes at the high dose. Increased absolute and/or relative weights in both sexes were considered adaptive and not adverse, since there were not histopathological correlates.

The LOAEL is 10000 ppm (295 mg/kg bw/day) in males and 7500 ppm (238 mg/kg bw/day)

in females, based on vomiting and clinical chemistry changes. The NOAEL is 1500 ppm in both sexes (45 mg/kg bw/day in males and 51 mg/kg bw/day in females).

This study is classified as **totally reliable** (**acceptable/guideline)** and satisfies guideline requirements for a 90-day oral toxicity study (OPPTS 870.3150; OECD 409) in non-rodents.

870.3200 21/28-Day Dermal Toxicity – Rat MRID 47923571

Dermal Administration of BAS 700 F (Batch: COD-001049; Purity: 99.2%) in a carboxymethylcellulose vehicle to 10/sex/dose Wistar rats (6 hours/day; 5 days/week, semi-occlusive dressing) for 4 weeks at dose levels of 0, 100, 300 and 1000 mg/kg bw/d caused no substance-related adverse findings.

An increase in absolute and relative liver weights in both sexes was possibly treatment related, Since there was neither a histopathological correlate nor any accompanying treatment-related changes of clinical chemistry parameters, this effect was not considered adverse.

The LOAEL in males and females was not identified. The NOAEL in males and females was 1000 mg/kg bw/day.

This study is classified as **totally reliable** (**acceptable/guideline)** and satisfies the guideline requirement for a dermal toxicity study (OPPTS 870.3200; OECD 410) in rats.

870.3465 90-Day Inhalation – Rat

- NA -

A.4.2 Prenatal Developmental Toxicity

870.3700a Prenatal Developmental Toxicity Study – Rat 47923603

BAS 700 F (Batch COD-000899, Purity 99.7%) was administered daily to presumably pregnant Crl:WI (Han) Wistar rats by oral gavage in a 0.5% carboxymethylcellulose vehicle during gestation days 6-19 at dose levels of 0, 25, 200 and 1000 mg/kg bw. The high dose of 1000 mg/kg bw/day resulted in increased (12-16%) absolute and relative thyroid weights (with correlating microscopic effects of thyroid hypertrophy and hyperplasia (considered adverse). Absolute and relative liver weights were increased significantly, but slightly (9-13%) at this dose and occurred in the absence of corroborating effects on serum liver enzymes (liver histopathology was not examined). This effect was considered as most likely due to hepatocellular hypertrophy (due to extensive evidence of hepatocellular hypertrophy in conjunction with increased liver weights throughout the database for this chemical) and so was not considered adverse.

The LOAEL for maternal toxicity in females is 1000 mg/kg bw/day, based on increased

absolute and relative thyroid weights and thyroid hypertrophy/hyperplasia. The NOAEL is 200 mg/kg bw/day.

No treatment-related effects on cesarean section parameters were observed at any dose. No treatment-related external, visceral or skeletal malformations were noted. BAS 700 F was not teratogenic up to the highest dose tested.

The LOAEL for developmental toxicity was not observed. The NOAEL is 1000 mg/kg bw/day.

This study is classified as **totally reliable (acceptable/guideline)** and satisfies guideline requirements for a prenatal developmental toxicity study (OPPTS 870.3700; OECD 414) in rats.

870.3700b Prenatal Developmental Toxicity Study – Rabbit MRID 47923604

A.4.3 Reproductive Toxicity

870.3800 Reproduction and Fertility Effects – Rat MRID 47923602

BAS 700 F (Batch COD-000899, Purity 99.7%) was administered daily to presumably pregnant Himalayan rabbits by stomach tube during gestation days 6-28 post insemination (p.i.) at dose levels of 0, 10, 25 and 60 mg/kg bw. The high of 60 mg/kg dose elicited signs of maternal toxicity as indicated by one abortion, decreased food consumption (-21.9% during the treatment period) corroborated by an increased number of animals with reduced or no defecation, body weight loss during gestation days 9 to 11 and a decrease of cumulative body weight gain by 49.3% during the treatment period. Body weighs were decreased 12% by Day 29, which was considered adverse. No maternal toxicity was observed at dose levels ≤ 25 mg/kg.

The LOAEL for maternal toxicity in males is 60 mg/kg bw/day, based on decreased body weight. The NOAEL is 25 mg/kg bw/day.

No treatment-related effects on cesarean section parameters were observed at any dose. No treatment-related external, visceral or skeletal malformations were noted. The only treatment-related variation was a statistically significant increase in incidence of mean % affected fetuses with paw hyperflexion at the high dose level (10.3%). This variation is frequently observed in control fetuses (up to 6.7% affected fetuses per study) and may reverse since tendons stretch postnatally as limbs grow and are being used. Although this variation occurred in presence of substantial maternal toxicity and so may be secondary to maternal toxicity, it was an effect of treatment and so is considered potentially adverse.

The LOAEL for developmental toxicity was 60 mg/kg bw/day, based on decreased fetal body weights and an increased incidence of paw hyperflexion, which was considered potentially adverse. The NOAEL is 25 mg/kg bw/day.

This study is classified as **totally reliable (acceptable/guideline)** and satisfies guideline requirements for a prenatal developmental toxicity study (OPPTS 870.3700; OECD 414) in rabbits.

A.4.4 Chronic Toxicity

870.4100b Chronic Toxicity – Dog MRID 47923570

BAS 700 F (Batch: COD – 001026, purity 99.4%) was administered to Beagle Dogs for 12 months at dietary dose levels of 0, 300, 1500 and 12000 ppm in males (0, 8, 39, and 335 mg/kg bw/day) and 0, 300, 1500 and 9000 ppm in females (0, 9, 43, and 257 mg/kg bw/day). Vomiting was observed in the all high dose animals at the beginning and midway through the study, and was considered adverse.

In the liver, changes in a number of clinical chemistry parameters at 1500 and/or 12000/9000 ppm as well as statistically significant changes of absolute and/or relative liver weights at 12000 ppm in males and 9000 ppm in females were observed. The clinical chemistry changes consisted of increased alkaline phosphatase, serum γglutamyl transferase, triglyceride and alanine-aminotransferase levels as well as decreased total protein, albumin, cholesterol, total bilirubin, creatinine, urea and calcium levels in either or both sexes. Histopathlogical analysis of the organ showed an intracytoplasmic iron deposition in hepatocytes as well as multifocal fibrosis (considered adverse) at dose levels of 1500 ppm and higher. One high dose male displayed a slight cirrhosis.

In the spleen, fine granular iron storage (distinct from hemosiderin) was observed at 1500 and 9000/12000 ppm. This was accompanied by a diffuse atrophy of the red pulp At 9000/12000 ppm. No histopathological changes were observed in the white pulp. The findings of iron storage and atropy at the high dose were considered potentially adverse.

Changes were also observed in the gall bladder (epithelial storage of granular brown pigment of males and females at ≥1500 ppm, not considered adverse) and the prostate (reduced weight and atrophy without change of the glandular structure at 12000 ppm, considered potentially adverse).

The LOAEL is 1500 ppm in females (43 mg/kg bw/day) based on hepatic fibrosis and clinical chemistry changes. The NOAEL in females in 9 mg/kd bw/day. The LOAEL in males is 12000 ppm (335 mg/kg bw/day) based on vomiting, clinical chemistry changes, and hepatic fibrosis and cirrhosis. The NOAEL in males is 1500 ppm (39 mg/kg bw/day).

This study is classified as **totally reliable** (**acceptable/guideline)** and satisfies guideline requirements for a chronic toxicity study (OPPTS 870.4100; OECD 452) in non-rodents.

A.4.5 Carcinogenicity

870.4300 Carcinogenicity/Chronic Study – Rat 47923591

BAS 700 F (Batches COD – 000899 up to study day 454 and COD-001049 from study day 455 to termination; Purity: 99.7% and 99.2%, respectively) was administered to Wistar rats at dietary dose levels of 0, 50, 250, 1500 and 3000 ppm (0/0, 2.1/2.7, 11/14, 68/82, or 145/182 mg/kg bw/day in males/females) for 2 years to assess carcinogenicity. A satellite group of animals was sacrificed at one year to assess chronic toxicity.

In the carcinogenicity group (50/sex/dose), body weight decreases after two years of 8% were noted in males at 3000 ppm. In females, body weights were decreased 11.9% or more at ≥ 250 ppm. This indicated that dosing was adequate. Treatment with BAS 700 F did not affect the survival of rats in the carcinogenicity group. Tumors considered a result of treatment were observed in the liver and thyroid only. Hepatocellular tumors were in the form of adenomas and carcinomas in both sexes, with a significant increase in the combined incidence of these tumor types in males at ≥ 1500 ppm and in females at 3000 ppm. Significant increases in hepatocellar carcinomas were observed only in males and only at 3000 ppm. Adenomas were observed in both sexes at a higher incidence than carcinomas and at lower doses. Significant increases in adenomas were observed in males at ≥ 1500 ppm and in females at 3000, ppm. However, adenoma incidence was greater than the upper limit of historical controls in males at ≥ 250 ppm and in females at ≥1500 ppm, and so was determined to be an effect of treatment. Non-neoplastic changes in the livers of these animals included increases in the absolute and relative liver weights of both sexes at ≥250 ppm in conjunction with centrilobular hepatocellular hypertrophy, spongiosis hepatitis in males at ≥1500 ppm, increased pigment storage (likely lipofucsin) in males and females at ≥1500 ppm, and dark brown liver discoloration at ≥1500 ppm.

Thyroid tumors resulting from treatment were in the form of follicular cell adenomas and carcinomas. The combined incidence of adenomas and carcinomas was significantly increased for males only at 3000 ppm compared to concurrent controls. The incidence was within the historical control range, but was still considered an effect of treatment. The individual incidence of thyroid follicular adenomas or carcinomas did not reach statistical significance for males or females. For males only, the incidence of carcinomas at 3000 ppm was not significantly different from concurrent controls, but was greater than the upper limit of the historical control values and so was considered treatment related. In males and females, the incidence of adenomas did not reach statistical significance at any dose compared to concurrent controls and was within the historical control range. These results were consistent with thyroid histopathology, which showed significant thyroid follicular hyperplasia in males at ≥1500 ppm. Colloid was also altered in both sexes at 1500 ppm and above.

In addition, the bones of animals in the carcinogenicity group were examined by gross and histopathology. In the femora and other bones of affected animals (nasal turbinates, sternae, vertebrae) deposition of Perl's Prussian Blue stain positive material, most probably iron, was

observed at ≥ 250 ppm in both sexes. No changes of the bone structure were identified by light microscopy. Gross pathological evaluation identified white discoloration of skull bones (frontal bone, dorsal skull, tympanic cavity) that diagnosed as periosteal hyperostosis (i.e. bone thickening). These effects were considered potentially adverse.

Chronic toxicity (one year duration) was also investigated in this study in satellite animals (10/sex/dose). Adverse effects on body weight were indicated by terminal body weights in both sexes at 3000 ppm that were decreased more than 10% relative to untreated controls. Increased absolute and relative liver weights were observed at ≥ 250 ppm in males and ≥ 500 ppm in females in conjunction with centrilobular hepatocellular hypertrophy at ≥ 1500 ppm in males and females, pigment storage (likely lipofucsin) in males and females at ≥ 1500 ppm, and liver discoloration at 3000 ppm in both sexes. None of these changes were considered clearly adverse. Changes in several clinical chemistry parameters were also observed. These consisted of increased serum □-glutamyl transferase (considered equivocal) in males and/or females at ≥ 1500 ppm, increased albumin and globulin in males and/or females at ≥ 1500 ppm, (not considered adverse), increased cholesterol and triglycerides in females at 3000 ppm (considered potentially adverse) decreased glucose in males at ≥ 250 ppm (not to a magnitude considered adverse), and decreased total biliribun in males and females at ≥ 250 ppm (not considered adverse). In addition, changes of electrolyte levels (Ca^{2+}, Cl^- and inorganic PO_4^{3-}) were observed in females and/or males, at 3000 ppm (PO_4^{3-} in males) and ≥ 1500 ppm (Ca^{2+}, Cl^- in males and females) but were not of a magnitude considered adverse. Also, in female livers a decrease of Perl's Prussian Blue stainable iron (as Fe^{3+}) was observed at ≥ 1500 ppm, which was not considered adverse.

The thyroid as well as the femur and other bones were also affected. In the thyroid an increased incidence of follicular cell hypertrophy/hyperplasia was observed in males at ≥ 1500 ppm. This was observed in conjunction with enlarged thyroid in all males at 3000 ppm. These thyroid effects were considered adverse. In the femora, deposition of Perl's Prussian Blue stain positive material, most probably iron, was observed. Although there were no light microscopically visible changes of the bone structure, this finding was considered to be potentially adverse. Discoloration of the teeth (incisors) was also observed in 3000 ppm males and females. This was not considered adverse.

Hematological changes were mainly restricted to female rats and consisted of slightly decreased hemoglobin, mean corpuscular volume and mean corpuscular hemoglobin concentrations at 1500 ppm and/or 3000 ppm. None of these effects were considered adverse. However, shorter prothrombin times were recorded for females at dose levels ≥ 250 ppm and in males at ≥ 1500 ppm, which were considered potentially adverse due to possible hypercoagulability.

The LOAEL for chronic toxicity in males is 250 ppm (11 mg/kg bw/day in males and 14 mg/kg bw/day in females) based on non-neoplastic changes in the liver (foci, masses) The NOAEL is 50 ppm (2.1 mg/kg bw/day in males and 2.7 mg/kg bw/day in females).

This study is classified as **totally reliable (acceptable/guideline)** and satisfies the guideline

requirement for a combined chronic toxicity/carcinogenicity study (OPPTS 870.4300; OECD 453) in rats.

870.4300 Carcinogenicity/Chronic Study – Mouse MRID 47923592

BAS 700 F (Batch COD–000899, Purity 99.7% up to study day 349; Batch COD-001049, Purity 99.2% from day 350 to end of study) was administered to C57BL/6 J Rj mice in the diet for 18 months at doses of 0, 150, 750, 3000 and 6000 ppm (21, 107, 468 and 996 mg/kg bw in males and 33, 158, 652 and 1307 mg/kg bw in females). There were no treatment-related neoplasms.

Systemic toxicity was observed as indicated by effects on body weight development in males at ≥ 3000 ppm and females at 6000 ppm. The liver was identified as the only target organ as indicated by increases of relative and/or absolute liver weights in males at ≥ 750 ppm and in females at ≥ 3000 ppm. Histopathological examination of the liver revealed mainly periportal (males; Zone 3) or peripheral (females; Zone 1) hepatocellular hypertrophy at 6000 ppm and ≥ 3000 ppm, respectively. This effect is not considered adverse. In addition, an increased severity and/or incidence of fatty changes in hepatocytes was observed at dose levels ≥ 750 ppm.

The LOAEL for chronic toxicity is 3000 ppm (468 mg/kg/day in males and 652 mg/kg/day in females) based on decreased body weight. The NOAEL is 750 ppm (158 mg/kg bw/day in males and 107 mg/kg bw/day in females).

This study is classified as **totally reliable (acceptable/guideline)** and satisfies the guideline requirement for a chronic toxicity/carcinogenicity study (OPPTS 870.4300; OECD 451) in mice.

A.4.6 Neurotoxicity

870.6100 Delayed Neurotoxicity Study-Hen-NA

870.6200a Acute Neurotoxicity MRID 47923605

The acute neurotoxicity of BAS 700 F (Batch COD-001026; Purity: 99.4%) was investigated in groups of 10 male and female Wistar rats (Crl:WI(Han) after a single administration by gavage at dose levels of 0, 125, 500, and 2000 mg/kg bw/d.

No signs of general systemic toxicity were observed. Treatment-related neurobehavioral effects were noted in mid and high dose animals only on the day of treatment. These consisted of slight, but statistically significant increase of the landing foot-splay in high dose males, reduction in the number of rearings in males at ≥ 500 mg/kg bw/d as well as impaired motor activity in high and mid dose males and females. No effects on these parameters were observed on study days 7 and 14. Additionally, no treatment-related neuropathological findings were noted, i.e. no brain weight changes or neurohistopathological findings were observed. Therefore, the affected clinical parameters were considered an indication of a neuropharmacological effect rather than an indication of neuronal damage.

The LOAEL is 500 mg/kg bw in males and females, based on decreased motor activity (in both sexes) and decreased rearing (in males only). The NOAEL is 125 mg/kg bw.

This study is classified as **totally reliable** (**acceptable/guideline)** and satisfies the guideline requirement for a an acute neurotoxicity study (OPPTS 870.6200; OECD 424) in rats.

870.6200b Subchronic Neurotoxicity MRID 47923606
Dietary administration of BAS 700F (Batch: COD-001026, Purity: 99.4%) to groups of 10 male and female Wistar Crl:WI(Han) rats at dietary dose levels of 0, 200, 1000, and 5000 ppm (11.5, 57.7, and 302.2 mg/kg body weight /day in males and 13.4, 67.2 and 337.7 mg/kg body weight/day in females) for 3 months did not result in any clinical (general clinical observation, FOB and motor activity) or neurohistopathological indication of neurotoxicity.

Signs of systemic toxicity observed in this study were consistent with those observed in other repeated dose rat studies with BAS 700 F. These consisted of slightly impaired body weight development in high dose females, changes of clinical chemistry parameters (increased serum □-GT, total protein, albumin, globulin, cholesterol, triglycerides, urea, Ca^{2+}, inorganic PO_4^- and Mg^{2+} levels as well as decreased AS(A)T, glucose and bilirubin levels), increased liver and thyroid weights as well as centrilobular hypertrophy of hepatocytes.

Under the conditions of the present study the no observed adverse effect level (NOAEL) for neurotoxicity was 5000 ppm, the highest dose tested, which is equivalent to about 302 mg/kg bw/d in males and 338 mg/kg bw/d in females.

The NOAEL for neurotoxicity is 5000 ppm (302 mg/kg bw/day in males and 338 mg/kg bw/day in females). The LOAEL was not observed.

This study is classified as **totally reliable** (**acceptable/guideline)** and satisfies the guideline requirement for a chronic neurotoxicity study (OPPTS 870.6200; OECD 424) in rats.
S**A.4.6 Mutagenicity MRIDs 47923572, 47923579, 47923577, 47923584**
MRID 47923572*S. typhimurium* and *E. coli* were exposed to BAS 700 F (Batch COD-001026; purity 99.4%) using dimethylsulfoxide (DMSO) as a solvent in the presence and absence of metabolic activation in two independent sets of experiments. Triplicate plates were used per dose and per test condition. Vehicle and positive controls were included in each experiment.

In the plate incorporation assay as well as in the preincubation test, BAS 700 F was tested up to the limit concentration of 5000 µg/plate. Concentrations of 20, 100, 500, 2500 and 5000 µg/plate were used with and without metabolic activation. In both the plate incorporation assay and the preincubation assay a weak bacteriotoxic effect was occasionally observed depending on the strain and test conditions at concentrations of 500 µg/plate (strain TA1537 in the plate incorporation assay) or above. Precipitation of the test substance was noted at concentrations of ≥ 500 µg/plate with and without metabolic activation in both experiments.

Neither in the first experiment (plate incorporation test) nor in the second experiment

(preincubation test) a biologically relevant increase in the number of revertant colonies was noticed in any of the strains tested in presence or absence of metabolic activation. The positive controls induced the appropriate response in the corresponding strains, thus demonstrating the sensitivity of the test system.

According to the results of the study, the test substance BAS 700 F is not mutagenic in the *Salmonella typhimurium/ Escherichia coli* reverse mutation assay under the experimental conditions of the study.

This study is classified as **totally reliable** (**acceptable/guideline)** and satisfies the guideline requirement for a bacterial reverse mutation test (OPPTS 870.5100, OECD 471).

MRID 47923579
BAS 700 F (Batch COD-000899; purity 99.7%) was tested *in vitro* for its ability to induce forward mutations in mammalian cells by assessing the mutation of the HPRT locus in Chinese Hamster CHO cells. Two independent sets of experiments were conducted in the presence and absence of metabolic activation. Based on the results of a preliminary cytotoxicity assay concentrations of 5 to 100 µg/mL were employed in the original experiment using a 4-hour exposure period with and without metabolic activation. In the second experiment concentrations of 6.3 to 100 µg/mL were used without metabolic activation for a 24 hour exposure and with metabolic activation for a 4 hour exposure. Ethylmethanesulfonate (EMS) and methylcholanthrene (MCA) served as positive controls in the experiments without and with metabolic activation, respectively. After the incubation period treatment media were replaced by culture medium and the cells were incubated for about one week for expression of mutant cells. This was followed by a 6 to 8 day incubation of cells in selection medium containing 6-thioguanine.

Cytotoxic effects indicated by reduced cloning efficiencies of below 20 % of the respective vehicle control were observed in both experiments with or without metabolic activation.

An increase in the mutant frequency was not observed neither in the original nor in the confirmatory study. The positive control substances, however, resulted in a marked increase in mutant frequency.

BAS 700 F does not induce forward mutations in mammalian cells *in vitro*, under the conditions of this study.

This study is classified as **totally reliable** (**acceptable/guideline)** and satisfies the guideline requirement for an *in vitro* gene mutation test (OPPTS 870.5300, OECD 476).

MRID 47923577
BAS 700 F (Batch COD-000899; purity 99.7%) was tested *in vitro* for the ability to induce chromosome and numerical aberrations in Chinese Hamster V79 cells in two independent experiments in the presence and absence of metabolic activation. Based on the cytotoxicity

results of a previously performed HPRT study, concentrations of 6.3 to 400 µg/mL were tested for clastogenic effects with and without metabolic activation in experiments with a pulse treatment of 4 hours or continuous treatment of 18 hours. The preparation intervals used were 18 h or 28 h after the beginning of treatment. Vehicle (DMSO) and positive controls (cyclophosphamide (CPP) and ethylmethanesulfonate (EMS) for the experiment with and without metabolic activation, respectively) were included to demonstrate the sensitivity of the test system.

Prior to cell harvest, addition of Colcemid arrested cells in the metaphase. After slide preparation and staining of the cells, at least 200 well spread metaphases per dose and treatment condition were analyzed for chromosomal aberrations.

At concentrations of 100 µg/mL and above a sufficient number of metaphases was not available for evaluation. Therefore, the highest concentration to be scored was 50 µg/mL. A relevant increase in the number of aberrant cells was not observed at any of the tested concentrations with or without metabolic activation. A confirmatory experiment was performed using a prolonged treatment and preparation interval (4 hours treatment and 24 hours recovery with S9-mix, 18 hours treatment and 0 hours or 10 hours recovery without S9-mix). In this experiment a slight increase above the historical control range was observed for the lowest evaluated concentration with metabolic activation only. This increase was not confirmed at higher concentrations and is, therefore, considered not relevant.

Based on the results of this study BAS 700 F is considered not to have a clastogenic potential *in vitro* in Chinese hamster V79 cells in the presence or absence of metabolic activation.

This study is classified as **totally reliable** (**acceptable/guideline)** and satisfies the guideline requirement for an *in vitro* chromosome aberration test (OPPTS 870.5375, OECD 473).

MRID 47923584
BAS 700 F (batch: COD-000826, purity: 99.6%) was tested for chromosomal damage (clastogenicity) and for the ability to induce spindle poison effects (aneugenic activity) in NMRI mice using the micronucleus test method. For this purpose, the test substance suspended in corn oil was administered twice orally within a 24-hour period to groups of 5 male mice at dose levels of 500, 1000, and 2000 mg/kg body weight in a volume of 10 mL/kg body weight. The vehicle served as negative and cyclophosphamide and vincristine sulfate as positive controls. The vehicle was administered twice at a 24 h interval and the positive controls once. The animals were sacrificed 24 hours after the last administration and the bone marrow of the two femora was prepared. After staining of the preparations, 2000 polychromatic erythrocytes were evaluated per animal and investigated for micronuclei. The normocytes with and without micronuclei occurring per 2000 polychromatic erythrocytes were also recorded.

Two oral administrations of BAS 700 F did not lead to any biologically relevant increase in the number of polychromatic erythrocytes containing either small or large micronuclei. The rate of micronuclei was mostly close to the concurrent negative control and was within the range of the

historical control data. Inhibition of erythropoiesis, determined from the ratio of polychromatic to normochromatic erythrocytes, did not occur. Signs of systemic toxicity were not observed up to the highest tested dose of 2000 mg/kg bw.

Both of the positive control chemicals, i.e. cyclophosphamide for clastogenic effects and vincristine for induction of spindle poison effects, led to the expected increase in the rate of polychromatic erythrocytes containing small (cyclophosphamide) or small and large (vincristine sulphate) micronuclei, thus demonstrating the sensitivity of the test system.

This study is classified as **totally reliable** (**acceptable/guideline)** and satisfies the guideline requirement for an erythrocyte micronucleus test (OPPTS 870.5395, OECD 474).

A.4.7

A.4.8 Metabolism

870.7485 Metabolism – Rat MRIDs 47923555 and 47923556

Biokinetic studies with ^{14}C–BAS 700 F (BASF Reg. Doc. # 2009/1074879) were performed to investigate plasma kinetics, mass balance, tissue distribution, urinary and fecal excretion, and biliary excretion. ^{14}C–BAS 700 F was administered to male and female Wistar rats (4/sex/dose) via oral gavage in a water/0.5% carboxymethylcellulose/1% cremophor vehicle. Plasma kinetics were first characterized by administering a single dose of 5, 50, or 500 mg/kg bw and plasma concentrations measured at 1, 2, 4, 8, 24, 48, 72, 96, 120, 144, and 168 hours. The times to maximum plasma levels (T_{MAX}) were 24 hours (500 mg/kg bw), 8 hours (50 mg/kg bw), and 1 hour (5 mg/kg bw) in both sexes with maximum mean plasma concentrations (C_{MAX}) of 65.31/66.08, 13.35/11.83, and 1.85/1.57 µg Eq/g in males/females, respectively. Areas Under Curve (AUCs) were 4215.2/5667.4, 434.6/532.4, 45.4/35.7 µg Eq h/g in males, females respectively. Importantly, no sex differences in the rate or extent of absorption was observed. Also, AUCs scaled with dose, indicating that absorption was not saturated and was most probably the result of passive diffusion. Although, the rates of elimination were the same in males and females in the time intervals following the Tmax, they were slightly reduced in females in the time interval immediately following the t_{max}. This could be due to the slight difference in tissue distribution between males and females and would explain the slightly higher AUCs in females at doses of 150 and 500 mg/kg bw and the difference in bile excretion pattern.

Doses of 150 and 7.5 mg/kg bw ^{14}C–BAS 700 F were chosen for mass balance, tissue distribution, and biliary excretion studies, based on the results of the plasma kinetic studies and repeated-dose toxicological studies. The duration of these studies (time to sacrifice) was based on the times of maximum plasma concentration (MPC), ½ MPC, ¼ MPC, and 1/8 MPC in each sex. In a tissue distribution study with single high and low doses, 150 mg/kg bw ^{14}C–BAS 700 F was administered orally (by gavage) to 4/sex/dose with males sacrificed at 16, 48, 72, and 96 hours and females sacrificed at 16, 56, 80, and 104 hours. The highest tissue concentrations of radioactivity in males and females were found at 16 hours. Radioactivity was widely distributed in both sexes with a similar pattern: the highest concentrations were found in the gut contents

and stomach contents. However, lower concentrations were found in numerous other organs/tissues, including the liver, thyroid, adrenal glands, kidney, pancreas, testes/uterus, and brain. For males and females, radioactivity declined in all tissues over time. In the single, low dose study, 7.5 mg/kg bw ^{14}C–BAS 700 F was administered orally (by gavage) to 4/sex/dose with males sacrificed at 1, 8, 28, and 48 hours and females sacrificed at 1, 20, 28, and 48 h after the administration of the test substance. A similar pattern of distribution of the radiolabel was observed as in the high dose group. Radioactivity declined in all tissues over time for the males and females except for the gut contents, which increased in 3-fold males from 1 hour to 8 hours prior to decreasing. A similar effect occurred in gut content in females, which increased from 1 to 20 hours about 1.5 fold up to 1.7-fold at 28 hours prior to decreasing at 48 h.

Mass balance and excretion were investigated in males and females in single dose studies with 150 or 7.5 mg/kg ^{14}C–BAS 700 F in animals with or without bile catheterization in 4 animals/sex/dose. Excreta and bile were collected in cannulated animals out to 72 hours, while excreta were collected in uncannulated animals out to 168 h. A subset of uncannulated animals (2 /sex/dose) were monitored in metabolic cages equipped to measure ^{14}C in expired air. A repeated-dose study was also performed in which males and females (4/sex) were administered 14 doses of unlabeled BAS 700 F one per day on Days 1-14 and ^{14}C–BAS 700 F on Day 15 with monitoring out to 168 hours after dose administration. Mean total recoveries of radioactivity were > 89% in males and females for all dose groups. For all dose groups, the majority of the administered radioactivity was excreted via feces (84.43–94.30% after 168 hours). The total amount of radioactivity excreted in urine after 168 hours was in the range of 3.47–16.7%. Non-relevant portions of the administered radioactivity were excreted as CO_2 in exhaled air. The time course of the amount of radioactivity found in urine and feces indicated the excretion occurred predominantly within three days after dosing, indicating low potential for bioaccumulation. Bile duct cannulation experiments showed that the bile was a major route of excretion. Within 72 hours after administration of ^{14}C–BAS 700 F at a dose level of 150 mg/kg bw, excretion via bile was found to be 58.86% and 63.19% of the administered radioactivity in males and females, respectively. Within 72 hours after administration of ^{14}C–BAS 700 F at a dose level of 7.5 mg/kg bw, excretion via bile was found to be 50.92% and 55.80% of the administered radioactivity in males and females, respectively. These data also demonstrated a gender–independent excretion pattern for ^{14}C–BAS 700 F.

Based on the amounts of radioactivity excreted via bile and urine, as well as the radioactive residue found in cage wash and carcass, the bioavailability of ^{14}C–BAS 700 F in rats was calculated to be about 65% and 67% of the applied dose for males and females at a dose of 150 mg/kg bw and about 68% and 80% of the applied dose for males and female rats at a dose level of 7.5 mg/kg bw.

This study is classified as **totally reliable** (**acceptable/guideline)** and, together with the metabolism study, satisfies the guideline requirement for a metabolism and pharmacokinetics study (OPPTS 870.7485; OECD 417) in rats.

The **metabolic fate** of ^{14}C–BAS 700 F was investigated in a follow-up study (BASF Reg. Doc. #

2009/1019789). Material from the biokinetics study was used for investigation of metabolite patterns in urine and feces (dose groups B, C, D) and in bile (dose groups R, S). Three additional groups of animals (designated DX, V, and W) were dosed with ^{14}C–BAS 700 F specifically for the metabolism study (see **Error! Reference source not found.Error! Reference source not found.**). Urine, plasma, and bile, as well as extracts of feces, liver, fat, and kidney tissue were analyzed by HPLC. Individual metabolites were detected down to a level of about 0.1% of the dose administered or less. Metabolites were identified by LC–MS and LC–MS/MS. The structures and codes of identified BAS 700 F metabolites are shown in **Error! Reference source not found.Error! Reference source not found.**.

In urine, 23 metabolites were identified. The main metabolites were in the range of 0.2% to 8.6% of the applied dose and identified to be M700F004, M700F005/M700F024 (detected only in male rats), M700F009/M700F028, M700F014, M700F015, and M700F061 (detected only in female rats). For all dose groups and both genders, no amounts of the unchanged parent compound were detectable at any of the time intervals investigated.

In feces, the unchanged parent compound was found to be the main constituent of the extracts at high dose levels, *i.e.*, dose group D, C, and DX (for both labels (19–44% of the dose applied), and represented only a minor part of the extractable radioactivity (3% of the dose applied) at the low dose level (dose group B). The main metabolites were identified as M700F009 (8–53% of the dose applied), M700F005 (ranging from 3–9% of the dose applied), and its isomer M700F006 (3–13% of the dose applied), and M700F016 (2–12% of the dose applied).

In bile, the main metabolites were in the range of 3.4 to 22.0% of the applied dose and identified to be M700F004 and its isomer M700F125, M700F009, M700F014 and its isomer M700F123, M700F005, M700F024, and M700F122.

In liver, the main metabolites were in the range of 0.1 to 0.9% of the applied dose and identified as M700F005, M700F006, M700F008, and M700F009. The parent compound was identified at levels up to 3.7 and 0.4% of the dose applied for the low and the high dose group, respectively.

In kidney, the main metabolite was identified to be M700F008 (0.02 to 0.11% of the applied dose). The active substance was present at levels up to 0.50 and 0.05% of the dose applied for the low and the high dose group, respectively.

In fat, two components were detected: the metabolite M700F008 (0.05 to 0.29% of the applied dose) and unchanged BAS 700 F (0.35 to 2.72% of the applied dose).

In plasma, the main metabolite was identified to be M700F006 (0.03 to 0.11% of the applied dose). The parent compound was present at levels up to 0.13 and 0.01% of the dose applied for the low and the high dose group, respectively.

The main biotransformation steps of BAS 700 F in rats are hydroxylation at the biphenyl ring system, N-demethylation at the pyrazole ring system, loss of a fluorine atom at the biphenyl ring

system, and conjugation with glucuronic acid or with glutathione derivatives. A further, but negligible transformation route is cleavage at the amide bond between the pyrazole ring system and the biphenyl ring system.

This study is classified as **totally reliable** (**acceptable/guideline)** and, together with the biokinetic study, satisfies the guideline requirement for a metabolism and pharmacokinetics study (OPPTS 870.7485; OECD 417) in rats.

870.7600 Dermal Absorption – Rat – MRID 47923632

^{14}C-BAS 700 F formulated as BAS 703 02 F, which contains both fluxapyroxad and pyraclostrobin (BAS 500F) was applied to the backs of male Crl:WI (Han) rats (4/dose/group) at nominal doses of 1670, 33.4, and 5.6 µg/cm^2 for 8 hours and protected with semi-occlusive dressing. Excreta were collected in metabolic cages over the exposure period. After the 8 hour exposure period, the dressing was removed and the skin of all animals was washed. In one group, animals were sacrificed and surface radioactivity removed with 2 tape strips prior to isolation of application site and surrounding skin and quantification of radioactivity in the carcass. For two post-observation groups, clean dressing was applied and the experiment continued out to 24 hours or 120 hours with continued collection of excreta. At the end of the post-observational period, dressings were removed and skin was washed and surface radioactivity removed with 2 tape strips prior to isolation of application site and surrounding skin and quantification of radioactivity in the carcass.

Average recoveries in all groups were acceptable and ranged from 88-105%. The majority of the radioactivity in all treatment groups was removed in the first skin wash, and ranged from 89-94%. Systemic absorption of radioactivity (the amount in the urine, feces cagewash, blood cells, plasma, and carcass) *increased* during over the post-observation period of 24-120 hours for all dose groups. Similarly, the amount of radioactivity in the skin at the application site and in the surrounding skin *decreased* over the post-observation period of 24-120 hours for all dose groups. Together, this indicates that skin-bound residue (pesticide that was not removed after the first wash, or that laterally diffused into the surrounding skin layers) was bioavailable and that the 120 hour post-observation period should be used for quantitative estimations of dermal absorption.

The amount of ^{14}C-BAS 700 F that was systemically absorbed at the end of the 120 hours post-observation period increased with decreasing dose, ranging from an average of 0.35% at 1670 µg/cm^2 to 7.81% at 5.6 µg/cm^2. Values at 5.6 µg/cm^2 were used to calculate a dermal absorption factor, which included the amount systemically absorbed (7.81%), the amount in the application site skin (0.50%), and the amount in the surrounding skin (0.07%) for a total dermal absorption factor that rounds to 8.4%. Inclusion or exclusion of the amount of ^{14}C-BAS 700 F on the skin (tape) strips does not changes this value.

This study is classified as **totally reliable** (**acceptable/guideline)** and satisfies the guideline requirement for a dermal penetration study (OPPTS 870.7600, OECD 427) in rats.

A.4.9 Immunotoxicity

870.7800 Immunotoxicity – Mouse MRID 47923633

The immunotoxic potential of BAS 700 F (Batch: COD-001049; Purity: 99.2%) in male C57BL/6J Rj mice (8/dose) was analyzed using dietary dose levels of 0, 500, 2000 and 6000 ppm (corresponding to approximate mean intake levels of 106, 450 and 1323 mg/kg/d, respectively) for 28 days.

Treatment with BAS 700 F did not result in systemic toxicity as assessed by clinical signs, food consumption and body weight development. The parameters used for detection of potential test substance related alterations in the morphology of the immune system included a) the determination of lymphoid organ weights (spleen and thymus) and b) the total lymphocyte count as well as lymphocyte subpopulation distribution including natural killer cells. Furthermore, functional parameters comprising of the analysis of the primary humoral (IgM response) immune response to sheep red blood cells (SRBC) and natural killer cell activity were integrated in this study. None of the parameters mentioned above was affected by treatment with BAS 700 F up to the highest dose level.

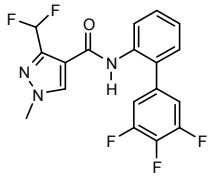
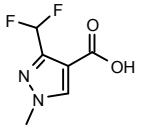
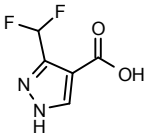
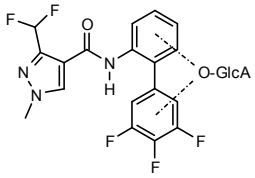
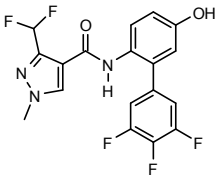
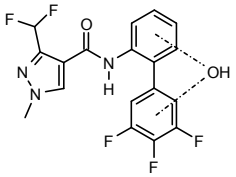
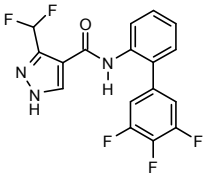
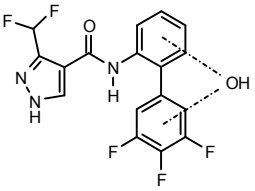
Concurrent treatment with positive control substance, cyclophosphamide (12 mg/kg bw/d by oral gavage) induced clear signs of immunotoxicity, demonstrating the reliability of the test system under the study conditions employed.

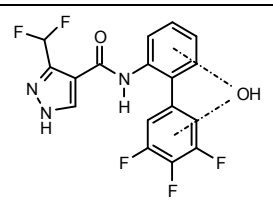
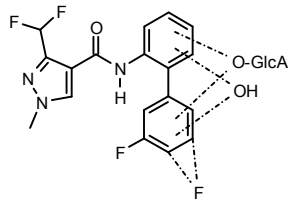
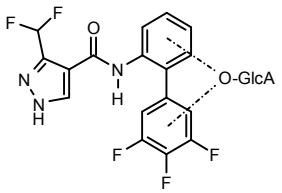
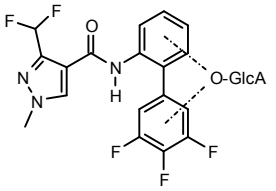
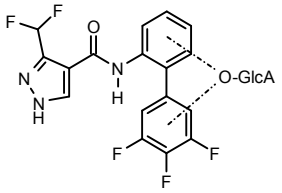
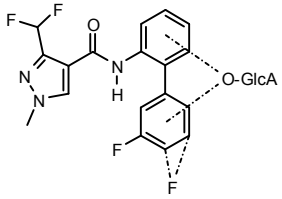
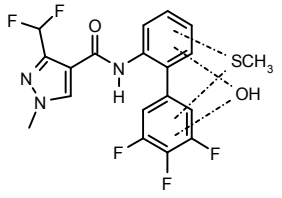
Based on the obtained results it can be concluded that BAS 700 F did not have an immunomodulatory/immunotoxic potential under the conditions of this study.

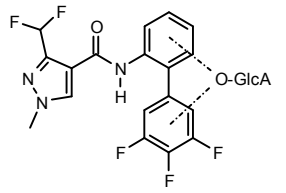
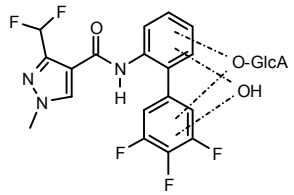
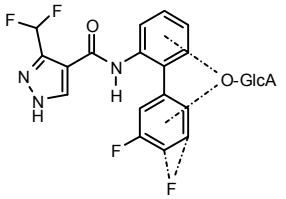
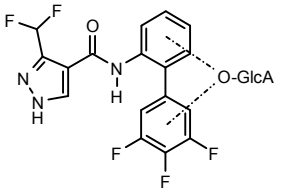
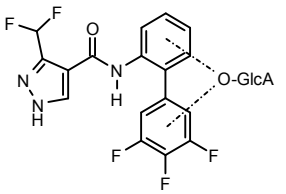
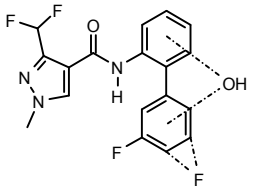
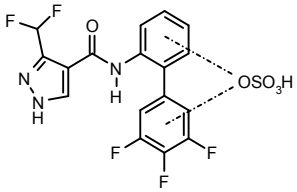
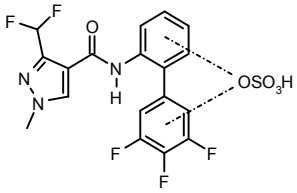
This study is classified as **totally reliable** (**acceptable/guideline)** and satisfies the guideline requirement (OPPTS 870.7800) for an immunotoxicity study.

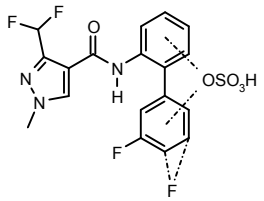
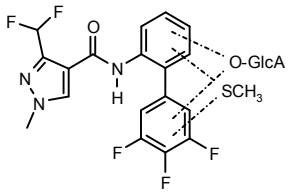
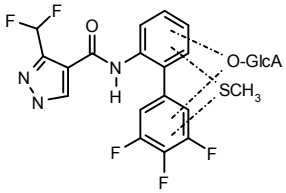
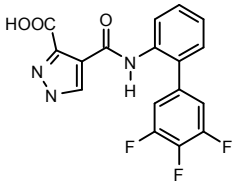
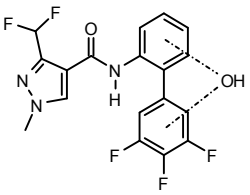
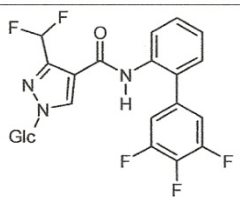
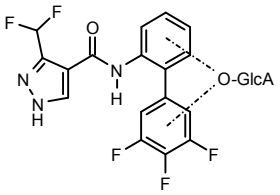
APPENDIX B. METABOLISM

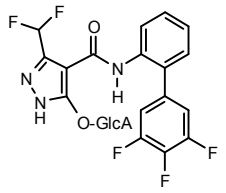
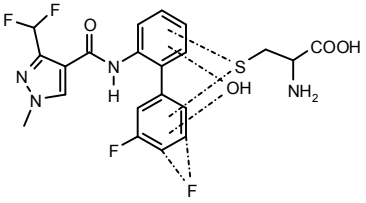
B. 1 Chemical Names and Structures

Metabolite Designation (Code) Chemical Name	Molecular Mass	Structure
BAS 700 F **=M700F000** 3-(difluoromethyl)-1-methyl-N-(3',4',5'-trifluoro[1,1'-biphenyl]-2-yl)-1Hpyrazole-4-carboxamide	M = 381	
M700F001 3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxylic acid	M = 176	
M700F002 3-(difluoromethyl)-1H-pyrazole-4-carboxylic acid	M = 162	
M700F004 3-(difluoromethyl)-1-methyl-N-((1-glucuronyl)oxy-3',4',5'-trifluoro-[1,1'-biphenyl]-2-yl -1H-pyrazole-4-carboxamide	M = 573	
M700F005 3-(difluoromethyl)-1-methyl-N-(4-hydroxy-3',4',5'-trifluoro[1,1'-biphenyl]-2-yl)-1H-pyrazole-4-carboxamide	M = 397	
M700F006 3-(difluoromethyl)-1-methyl-N-(hydroxy-3',4',5'-trifluoro[1,1'-biphenyl]-2-yl)-1H-pyrazole-4-carboxamide	M = 397	
M700F008 3-(difluoromethyl)-N-(3',4',5'-trifluoro[1,1'-biphenyl]-2-yl)-1H-pyrazole-4-carboxamide	M = 367	
M700F009 3-(difluoromethyl)-N-(hydroxy-3',4',5'-trifluoro[1,1'-biphenyl]-2-yl)-1Hpyrazole-4-carboxamide	M = 383	

M700F010 3-(difluoromethyl)-N-(hydroxy-3',4',5'-trifluoro[1,1'-biphenyl]-2-yl)-1Hpyrazole-4-carboxamide	M = 383	
M700F011 3-(difluoromethyl)-1-methyl-N-(hydroxy-(1-glucuronyl)oxy-3',[4' or 5']-difluoro-[1,1'-biphenyl]-2-yl)-1H-pyrazole-4-carboxamide	M = 571	
M700F012 3-(difluoromethyl)-N-((1-glucuronyl)oxy-3',4',5'-trifluoro-[1,1'-biphenyl]-2-yl)-1H-pyrazole-4-carboxamide	M = 559	
M700F013 3-(difluoromethyl)-1-methyl-N-((1-glucuronyl)oxy-3',4',5'-trifluoro-[1,1'-biphenyl]-2-yl)-1H-pyrazole-4-carboxamide	M = 573	
M700F014 3-(difluoromethyl)-N-((1-glucuronyl)oxy-3',4',5'-trifluoro-[1,1'-biphenyl]-2-yl)-1H-pyrazole-4-carboxamide	M = 559	
M700F015 3-(difluoromethyl)-1-methyl-N-((1-glucuronyl)oxy-3',[4' or 5']-difluoro-[1,1'-biphenyl]-2-yl)-1H-pyrazole-4-carboxamide	M = 555	
M700F016 3-(difluoromethyl)-1-methyl-N-(methylthio-hydroxy-3',4',5'-trifluoro-[1,1'-biphenyl]-2-yl)-1H-pyrazole-4-carboxamide	M = 443	

M700F019 3-(difluoromethyl)-1-methyl-N-((1-glucuronyl)oxy-3',4',5'-trifluoro-[1,1'-biphenyl]-2-yl)-1H-pyrazole-4-carboxamide	M = 573	
M700F020 3-(difluoromethyl)-1-methyl-N-(hydroxy-(1-glucuronyl)oxy-3',4',5'-trifluoro-[1,1'-biphenyl]-2-yl)-1H-pyrazole-4-carboxamide	M = 589	
M700F021 3-(difluoromethyl)-N-((1-glucuronyl)oxy-3',[4' or 5']-difluoro-[1,1'-biphenyl]-2-yl)-1H-pyrazole-4-carboxamide	M = 541	
M700F022 3-(difluoromethyl)-N-((1-glucuronyl)oxy-3',4',5'-trifluoro-[1,1'-biphenyl]-2-yl)-1H-pyrazole-4-carboxamide	M = 559	
M700F023 3-(difluoromethyl)-N-((1-glucuronyl)oxy-3',4',5'-trifluoro[1,1'-biphenyl]-2-yl)-1H-pyrazole-4-carboxamide	M = 559	
M700F024 3-(difluoromethyl)-1-methyl-N-(hydroxy-3',[4' or 5']-difluoro[1,1'-biphenyl]-2-yl)-1H-pyrazole-4-carboxamide	M = 379	
M700F025 3-(difluoromethyl)-N-((hydroxysulfonyl)oxy-3',4',5'-trifluoro[1,1'-biphenyl]-2-yl)-1H-pyrazole-4-carboxamide	M = 463	
M700F026 3-(difluoromethyl)-1-methyl-N-((hydroxysulfonyl)oxy-3',4',5'-trifluoro[1,1'-biphenyl]-2-yl)-1H-pyrazole-4-carboxamide	M = 477	

M700F027 3-(difluoromethyl)-1-methyl-N-((hydroxysulfonyl)oxy-3',[4' or 5']-difluoro[1,1'-biphenyl]-2-yl)-1H-pyrazole-4-carboxamide	M = 459	
M700F028 3-(difluoromethyl)-1-methyl-N-(methylthio-(1-glucuronyloxy)-3',4',5'-trifluoro-[1,1'-biphenyl]-2-yl)-1H-pyrazole-4-carboxamide	M = 619	
M700F029 3-(difluoromethyl)-N-(methylthio-(1-glucuronyl)oxy- 3',4',5'-trifluoro-[1,1'-biphenyl]-2-yl)-1H-pyrazole-4-carboxamide	M = 605	
M700F032 3-(hydroxycarbonyl)-N-(hydroxy-3',4',5'-trifluoro[1,1'-biphenyl]-2-yl)-1H-pyrazole-4-carboxamide or tautomer	M = 361	
M700F042 3-(difluoromethyl)-1-methyl-N-(hydroxy-3',4',5'-trifluoro[1,1'-biphenyl]-2-yl)-1H-pyrazole-4-carboxamide	M = 397	
M700F048 3-(difluoromethyl)-1-(-D-glucopyranosyl)-N-(3',4',5'-trifluoro[1,1'-biphenyl]-2-yl)-1H-pyrazole-4-carboxamide		
M700F050 3-(difluoromethyl)-N-((1-glucuronyl)oxy-3',4',5'-trifluoro[1,1'-biphenyl]-2-yl)-1H-pyrazole-4-carboxamide	M = 559	

M700F061 3-(difluoromethyl)-5-(1-glucuronyl)oxy-N-(3',4',5'-trifluoro[1,1'-biphenyl]-2-yl)-1H-pyrazole-4-carboxamide	M = 559	
M700F063 3-(difluoromethyl)-1-methyl-N-((S-cysteinyl)-hydroxy-3',[4' or 5']-difluoro-[1,1'-biphenyl]-2-yl)-1H-pyrazole-4-carboxamide	M = 498	

B.2 METABOLISM SUMMARY TABLE

Table B.2 Tabular Summary of Fluxapyroxad Metabolites and Degradates			
Chemical Name (other names in parenthesis) and Structure	**Matrix**	**Percent TRR (PPM) [1]**	
		Matrices - Major Residue (>10%TRR)	**Matrices - Minor Residue (<10%TRR)**
Parent - Fluxapyroxad	Soybean forage TRR 4.1-6.1 ppm	Parent >92%	M700F048 0.6-1.2%
	Soybean hay TRR 61-64 ppm	Parent 88%	M700F048 1.6-2.2%
	Soybean straw TRR 0.85-1.2 ppm	Parent 92%	M700F048 0.8%
	Soybean hull TRR 2.2-3.3%	Parent 64%	M700F048 2.6-3.1% M700F002 ND-2%
	Soybean seed TRR 0.11-0.24 ppm	Parent 21% (TRR ~0.12) M700F002 ND-33% M700F048 9-20%	
	Tomato leaves TRR 4.4-6.7 ppm	Parent >90%	M700F075/M700F076 <1.4% M700F048 <0.8% M700F008 2.8%
	Tomato fruit TRR 0.12-0.16 ppm	Parent >94%	M700F008 <1.4%
	Wheat forage TRR 0.9-1.0 ppm	Parent 87-91%	M700F008 et al 4.2-5.8%
	Wheat hay TRR 10 ppm	Parent 87-89%	M700F008 et al 2.4-3.3%
	Wheat straw TRR 17-19 ppm	Parent 84-86%	M700F008 et al 2.8-3.7%
	Wheat chaff TRR 6.7-7.4 ppm	Parent 76-82%	M700F008 et al 5.8-6.2%
	Wheat grain TRR 0.045-0.057 ppm	Parent 60-63%	M700F008 et al 6.5%
	Rotational Crops		
	Rotational spinach 30 day TRR 0.10/0.18 ppm	Parent 10-22% M700F002 48% M700F058 11.5% M700F074 4.7-16.4%	M700F001 1.0% M700F008 3.1-4.9% M700F036 7.8% M700F042 4.2-8.1% M700F048/M700F057 4.5%
	Rotational Radish Top 30 day TRR 0.069/-- ppm	Parent 18% M700F008 24% M700F048/M700F057 13% M700F059 11%	M700F036 9% M700F042 0.7% M700F058 0.9% M700F074 3.3%
	Rotational Radish Root 30 day; TRR 0.015/0.014 ppm	Parent 43-53% M700F008 26-29%	M700F048/M700F057 4.9-5.9%

Table B.2 Tabular Summary of Fluxapyroxad Metabolites and Degradates			
Chemical Name (other names in parenthesis) and Structure	**Matrix**	**Percent TRR (PPM) [1]**	
		Matrices - Major Residue (>10%TRR)	**Matrices - Minor Residue (<10%TRR)**
	Rotational Wheat forage 30 day TRR 0.14/0.28 ppm	Parent 76-84%	M700F002 4.2% M700F008 5.6-6.0% M700F036 0.6% M700F048/M700F057 1.0% M700F074 1.0%
	Rotational Wheat hay 30 day TRR 1.08/-- ppm	Parent 81%	M700F008 6.2% M700F042 0.6% M700F048/M700F057 0.9%
	Rotational Wheat straw 30 day TRR 1.88/2.7 ppm	Parent 54-64%	M700F002 2.0% M700F008 4.4-7.6% M700F042 0.9-6.0% M700F048/M700F057 1.9-2.2% M700F074 2.4%
	Rotational Wheat chaff 30 day TRR 0.40/1.1 ppm	Parent 54-64%	M700F001 0.7% M700F002 5.9% M700F008 7.8% M700F042 0.3-0.5% M700F058 1.7% M700F074 3.1%
	Rotational Wheat grain 30 day TRR 0.02/0.03 ppm	Parent 24-28%	M700F008 4.0-6.4% M700F042 0.3%
	Ruminant milk TRR 0.011/0.017 ppm	Parent 13-20% M700F008 24-25% M700F010/M700F040 12-15%	M700F009 5.5-5.7%
	Ruminant liver TRR 0.35/0.56 ppm	M700F008 13-17%	Parent 3.2-3.7% M700F004 1.9-2.6% M700F005/M700F024 6.4-8.3% M700F009 2.3-2.5% M700F010/M700F040 0.7%
	Ruminant kidney TRR 0.036/0.078 ppm	M700F004 12-13% M700F008 22-26% M700F005/M700F024 5.2-19%	Parent 5.4-7.0% M700F009 2.0-3.6% M700F010/M700F040 3.1-4.0% M700F014 3.0-3.5% M700F015 4.1-5.2% M700F034/M700F036 4.9-5.2% M700F038/M700F039 5.1-9.0% M700F046/M700F047 3.1-4.4%
	Ruminant muscle TRR 0.007 ppm	Parent 12% M700F008 55-83%	
	Ruminant fat	Parent 34-44%	M700F004 ND-6.1%

Table B.2 Tabular Summary of Fluxapyroxad Metabolites and Degradates			
Chemical Name (other names in parenthesis) and Structure	**Matrix**	**Percent TRR (PPM) [1]**	
		Matrices - Major Residue (>10%TRR)	**Matrices - Minor Residue (<10%TRR)**
	TRR 0.021/0.025 ppm	M700F008 26% M700F005/M700F024 3.2-14%	M700F010/M700F040 ND-3.7%
	Ruminant urine TRR 1.9/4.3 ppm	M700F005/M700F024 33-34% M700F008 14-36% M700F046/M700F047 9.3-10.3%	M700F004 1.3% M700F009 8.8% M700F010/M700F040 2.6-3.0% M700F034/M700F036 1.3-6.2% M700F038/M700F039 2.5-2.8% M700F041/-42/-43/-44 2.6-3.6%
	Ruminant feces TRR 1.9/1.8 ppm	M700F005/M700F024 35-50%	Parent 2.0-4.0% M700F008 ND-7.8% M700F033 ND-1.4%
	Ruminant bile TRR 7.3/6.6 ppm	M700F004 55% M700F014 25% M700F015 10%	M700F112 0.8%
	Poultry liver TRR 0.21 ppm		Parent 1% M700F005 4.1% M700F008 4.1% M700F008/ M700F038 5.3% M700F024 6.9% M700F0047 3.1%
	Poultry muscle TRR 0.010 ppm	Parent 12% M700F008 17% Dimer of parent 21%	M700F005 2.8%
	Poultry fat TRR 0.059 ppm	Parent 38% M700F008 15% Dimer of parent 36%	M700F005 1%
	Poultry eggs TRR 0.077 ppm	Parent 12% M700F008 44% Dimer of parent 36%	M700F004 4.2% M700F005 6.6% M700F009/ M700F038 5.0%
	Poultry excreta TRR 3.64 ppm	M700F005 17% M700F024 11% M700F009/ M700F038 12%	Parent 7.4% M700F008 6.3% M700F047 3.7% Dimer of parent 1.1%
	Rat liver Dose 150 mg/kg	Parent 0.16-0.36% M700F008 0.17-0.45% M700F006 0.18-0.23% M700F005 0.10-0.19% M700F009 0.12-0.17%	M700F010 et al 0.02-0.04% M700F016 0.01-0.04% M700F0240.06
	Rat kidney Dose 150 mg/kg		M700F008 0.0-0.5% Parent 0.03-0.05%
	Rat fat	Parent 0.35-1.55	M700F006 0.03-0.09%

Table B.2 Tabular Summary of Fluxapyroxad Metabolites and Degradates			
Chemical Name (other names in parenthesis) and Structure	**Matrix**	**Percent TRR (PPM) [1]**	
		Matrices - Major Residue (>10%TRR)	**Matrices - Minor Residue (<10%TRR)**
	150 mg/kg	M700F008 0.040.25%	
	Rat Feces 150 mg/kg	M700F009 9-11% Parent 30-31%	M700F005 2.7-5.2% M700F006 6.2-7.8% M700F008 0.34% M700F010 1.7-3.2% M700F016 4.2-9.5%
	Water		
	Water		

Summary of Metabolism Studies

Soybean; PMRA# 1883838. MRID 47923642.; Application Rate: 3 applications x 60 g a.i./ha (0.6x single rate; 0.9x seasonal rate) at BBCH 16/17, 51–59 and 71–75; 0.6x compared to single application rate; pre-harvest interval 14 day PHI for mature forage (from 2d treatment); 30 day PHI for soybean hay, straw, hull and seed. BASF only attempted to identify parent, M700F0002, and M700F048.

Tomato; PMRA# 1883840. MRID 47923641. Application Rate: 3 x 100 g a.i./ha (1x rate). The applications took place 17, 10 and 3 days before harvest (55, 62 and 69 days after planting). Tomato fruits and leaves were sampled three days after the last treatment.

Wheat; PMRA# 1883842. MRID 47923643.2 applications x 125 g a.i./ha (1.25x). Wheat hay was sampled at 4 DALA; straw, chaff and grain samples were collected at 34-35 DALA. Wheat forage samples were collected 36 days after the first application (forage samples received one application of 125 g a.i./ha only).

Rotational Crops (spinach, radish and wheat); PMRA# 1884199. MRID 47923680; One application 250 g a.i./ha (2.5x single rate, 0.83x seasonal rate). The treated soil was aged for 30, 120 and 365 days.

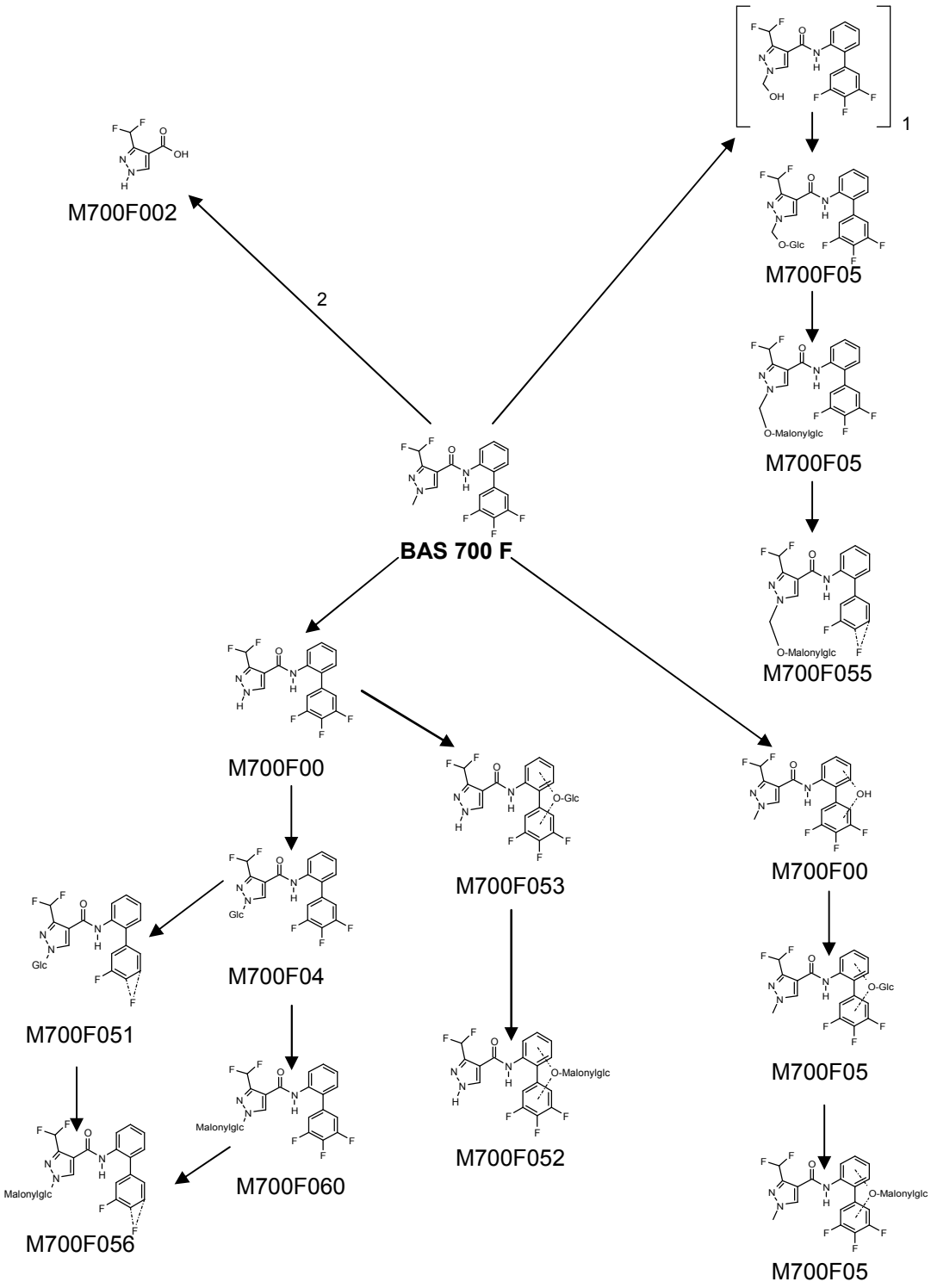
Lactating Goat ; PMRA# 1883854 (full report). MRID 47923649.; 12 mg/kg Feeding Level; Level of exaggeration compared to maximum dietary burden: 2.6x Beef cattle dietary burden; 0.55x dairy cattle dietary burden; 8 days of dosing; 24 hour pre-slaughter interval.

Poultry; Study report. PMRA# 1883852 (full report). MRID 47923645 12 mg/kg Feeding Level; Level of exaggeration compared to maximum dietary burden: 3.2x poultry dietary burden; 12 days of dosing; 23 hour pre-slaughter interval.

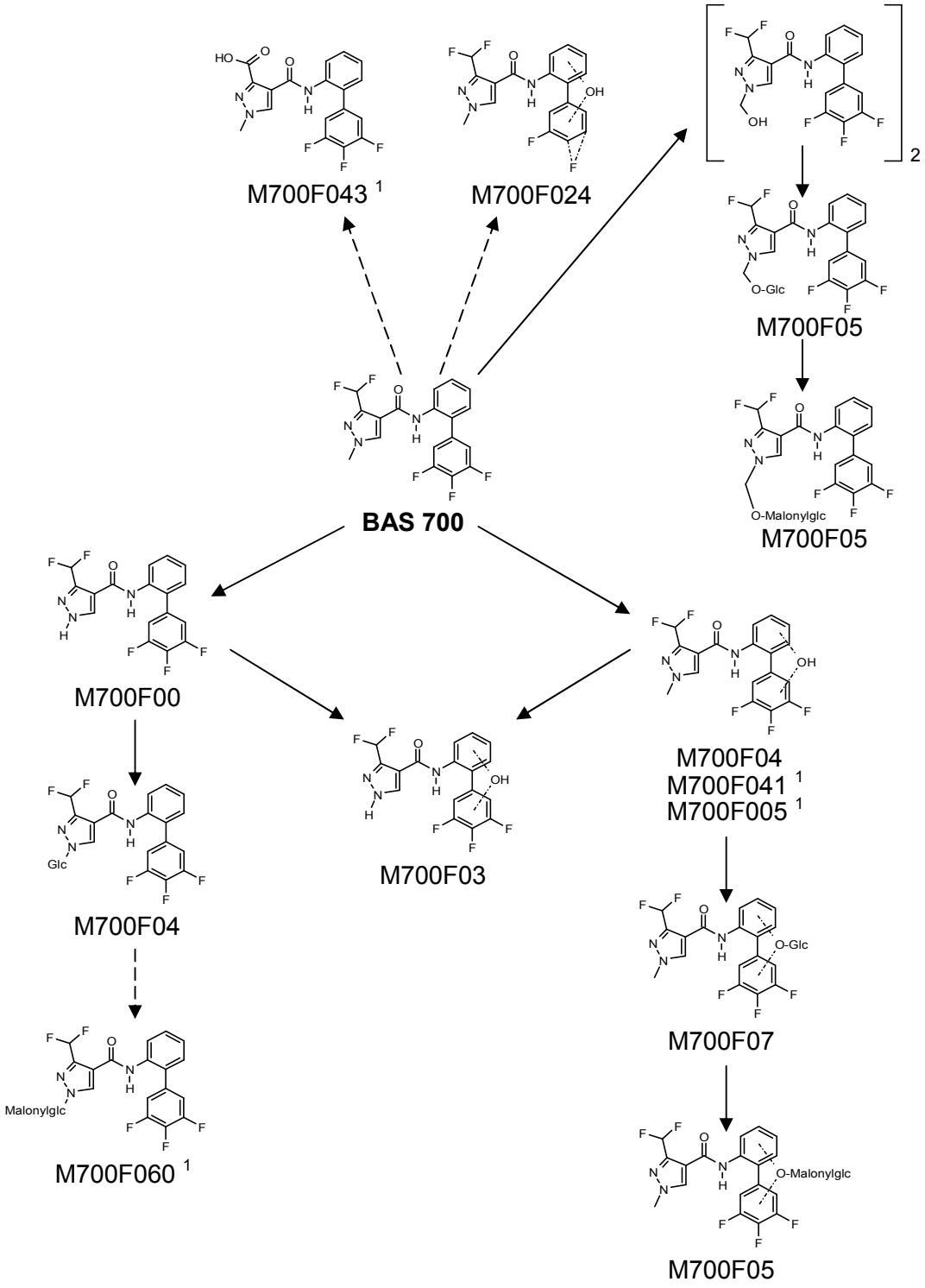
Rat; Strain: Wistar Crl: WI (Han); male/female; MRID 47923556; BASF Reg. Doc. # 2009/1019789; 150 mg/kg dosing level; percentages reported are percent of administered dose. Route of Administration: Oral: gavage; Vehicle: 0.5% aqueous solution of CMC (carboxymethyl cellulose) containing 1% Cremophor

B.3 METABOLIC PATHWAYS

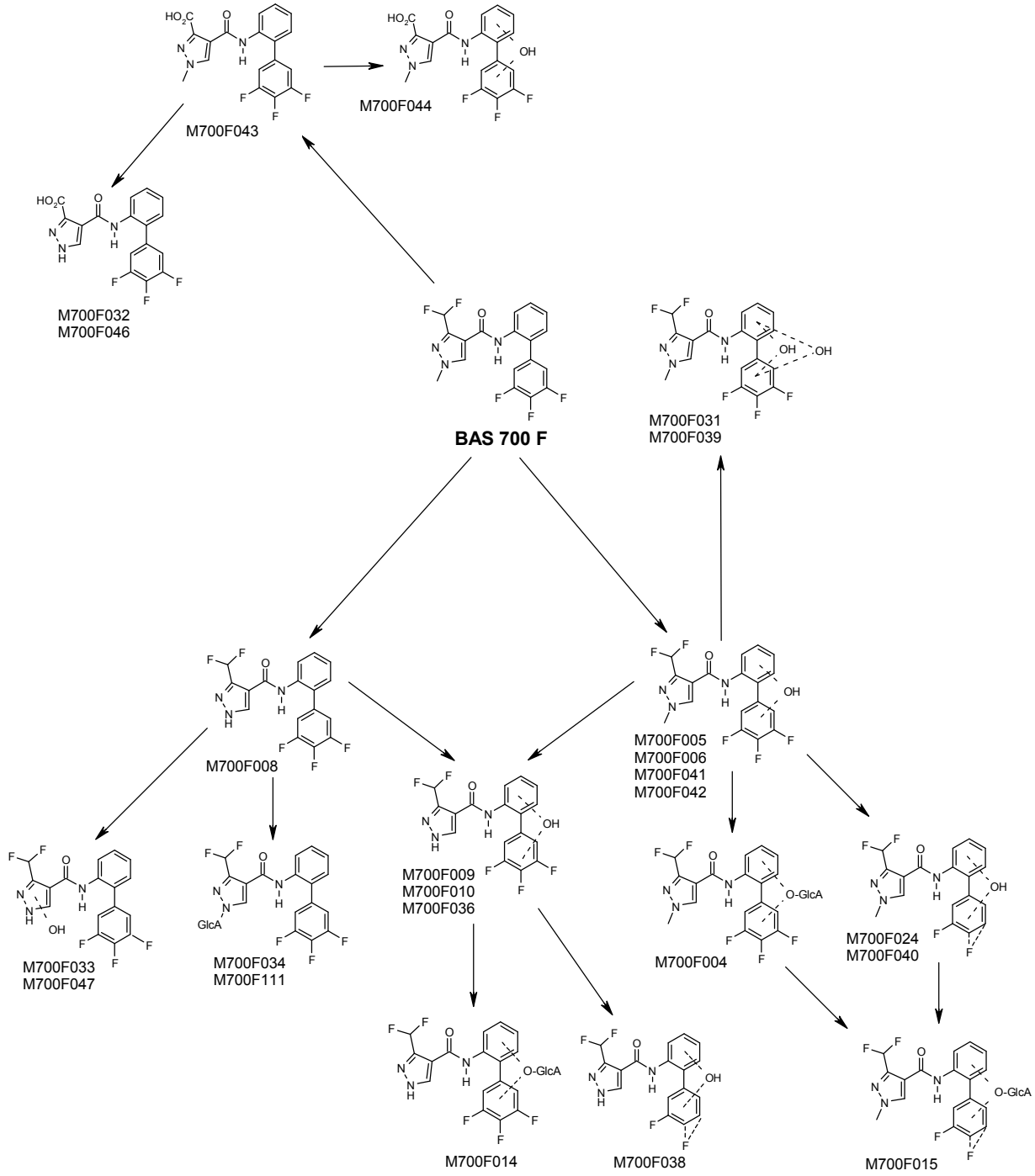
Proposed metabolic pathways of BAS 700 F (fluxapyroxad) in plants.



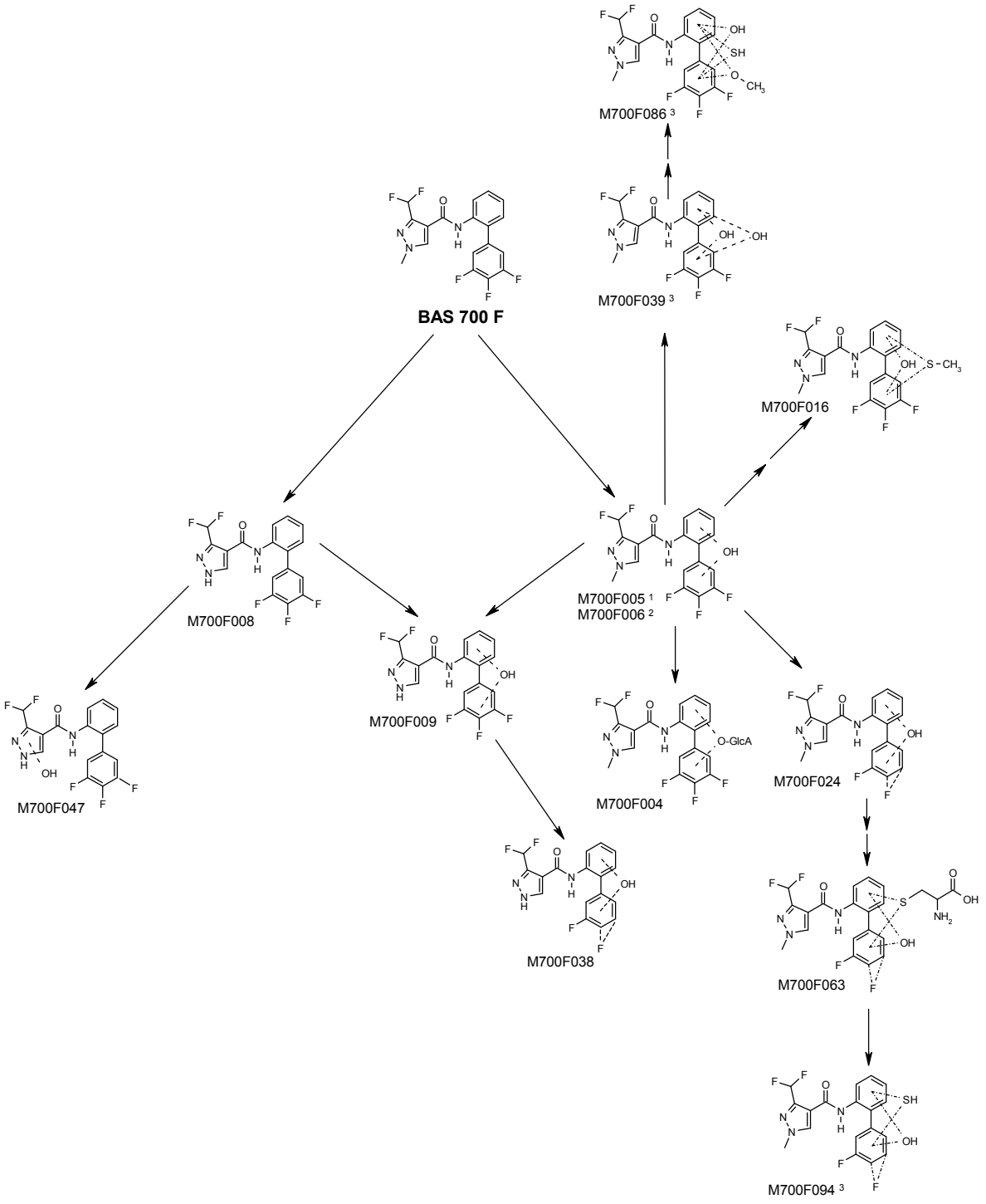
Proposed metabolic pathways of BAS 700 F (fluxapyroxad) in rotational crops (aniline label).



Proposed metabolic pathways for BAS 700 in lactating goats.



Proposed metabolic pathways of BAS 700 F in laying hens.

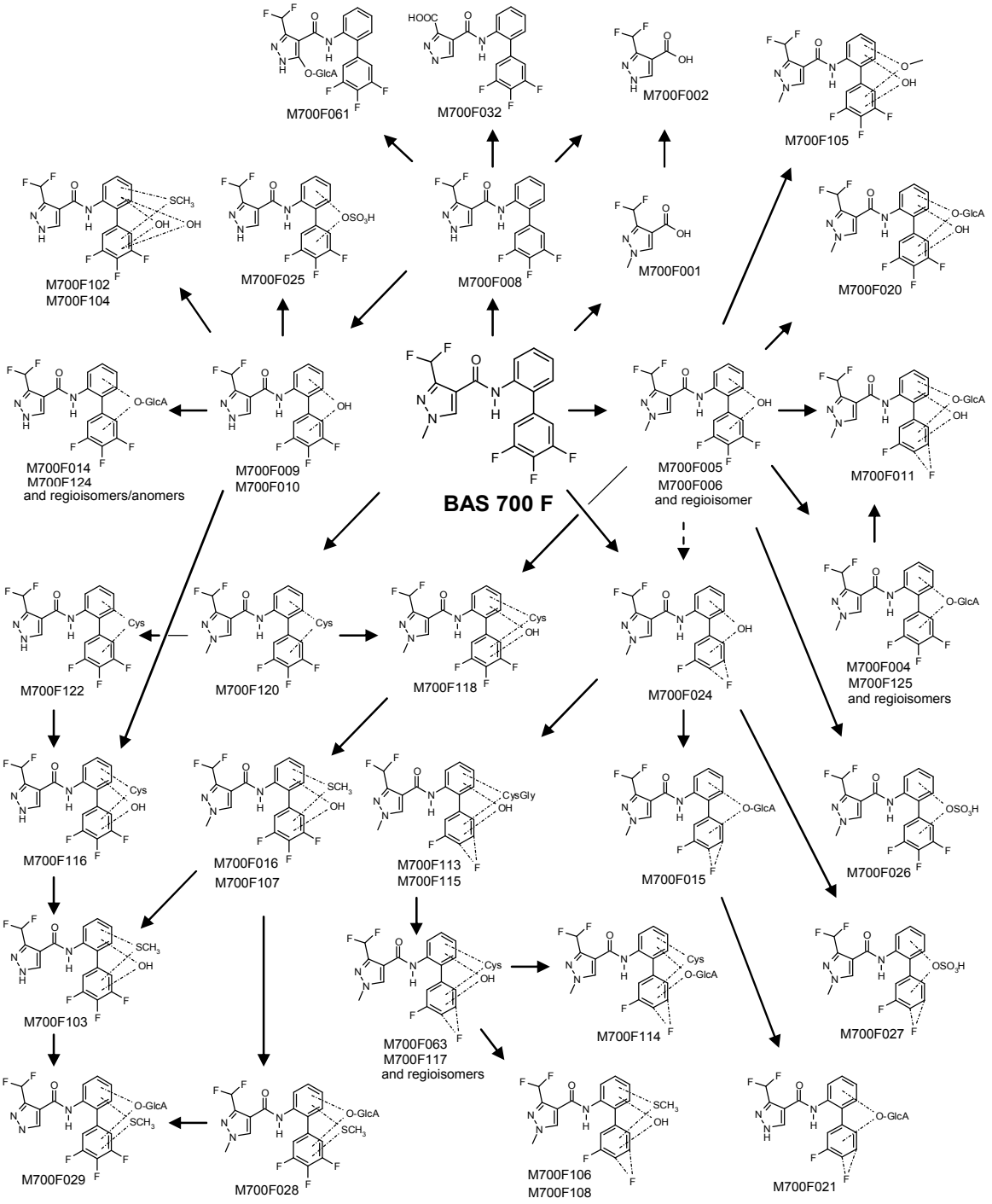


[1] M700F005 is hydroxylated in para-position to the amide group, established by ^{1}H NMR spectroscopy

[2] Proposed intermediate, not identified in the current study

[3] These metabolites were identified by LC-MS/MS, but they could not unambiguously be assigned to a distinct HPLC peak. They occurred at minor quantities, but they were not listed in metabolite quantification tables, because the correlation to a distinct HPLC peak was not given.

Proposed Metabolic Pathway of BAS 700 F in the Rat



Remark: CysGlyc = cysteineglycine, Cys = cysteine; GlcA = glucuronic acid

APPENDIX C. PHYSICAL/CHEMICAL PROPERTIES

TABLE 2. Physicochemical Properties of Fluxapyroxad

Parameter	Value	Reference
Melting point/range	156.8 °C	Product Chemistry monograph B.
pH of 1% solution in water	5.8	
Density	1.47	
Water solubility (20°C)	3.88 mg/L at pH 5.8 (not buffered) 3.78 mg/L at pH 4 3.44 mg/L at pH 7 3.84 mg/L at pH 9	
Solvent solubility (g/L at 20°C)	acetone >250 acetonitrile 167.6 ± 0.2 dichloromethane 146.1 ± 0.3 ethylacetate 123.3 ± 0.2 methanol 53.4 ± 0.0 toluene 20.0 ± 0.0 n-octanol 4.69 ± 0.01 n-heptane 0.106 ± 0.001	
Vapor pressure at 25 °C	8.1×10^{-9} Pa	
Dissociation constant (pK_a)	12. 58 (calculated)	
Octanol/water partition coefficient Log(K_{OW})	3.08 (deionized water) 3.09 at pH 4 3.13 at pH 7 3.09 at pH 9	
UV/visible absorption spectrum	pH 1.4: λmax 199, ε 35913; 230, 24137; 290, 1145 pH 5.9: λmax 193, ε 44100; 230, 24010; 290, 978 pH 12.2: λmax 215, ε 23227; 229, 23473; 290, 2405 ε: molar absorption coefficient, [L mol^{-1} cm^{-1}]	

APPENDIX D. REVIEW OF HUMAN RESEARCH

The PHED Task Force, 1995. The Pesticide Handlers Exposure Database, Version 1.1. Task Force members Health Canada, U.S. Environmental Protection Agency, and the National Agricultural Chemicals Association, released February, 1995.

Agricultural Re-entry Task Force (ARTF) data base (SOP #3.1)