Health Canada Santé Canada

Evaluation Report for Category B, Subcategory 5.0 Application

Application Number: 2013-6151
Application: New maximum residue limit for previously assessed technical grade active ingredient
Product: Fluazifop-P-butyl Technical
Registration Number: 21208
Active ingredients (a.i.): Fluazifop-P-butyl
PMRA Document Number: 2556817

Background

Fluazifop-P-butyl is currently registered in Canada for use in/on agricultural food/feed and ornamentals. Fluazifop-P-butyl is a post-emergent herbicide for control of perennial and annual grass weeds in broadleaf crops.

Purpose of Application

The purpose this application for Fluazifop-P-butyl Technical (Registration Number 21208) was to:

1) To revise the maximum residue limit (MRL) on imported sweet potato roots from 0.5 ppm to 1.5 ppm to align with the US tolerance based on the new field residue trials, and

2) To establish MRLs on imported citrus crops and processed commodities.

Chemistry, Environment and Value Assessments

Chemistry, environment and value assessments were not required for this application.

Health Assessments

The PMRA conducted a detailed review of new oral toxicology data submitted to update the toxicology database and risk assessment of the Fluazifop-P-butyl Technical. The new studies consisted of an acute oral toxicity study in rats, an acute dermal toxicity study in rabbits, a 90-day dietary toxicity study in hamsters, two developmental toxicity studies in rats using fluazifop-P-butyl, and a toxicokinetic study using fluazifop-butyl (FB) in mice. The toxicity of the fluazifop-P-butyl metabolite, 5-(trifluoromethyl)-2-pyridinone (Compound 10), was also evaluated based on a toxicokinetic study, an acute oral toxicity study, a 28-day dietary toxicity study in rats, a developmental toxicity study in rats, and a battery of genotoxicity studies. Although sufficient for regulation, previously submitted studies had some limitations regarding dose selection.

Canada

The newly submitted studies allowed for further assessment of the sensitivity of the young and a toxicological characterisation of metabolite Compound 10. The database is complete, consisting of the full array of toxicity studies currently required for regulatory purposes. The studies were carried out in accordance with currently accepted international testing protocols and good laboratory practice. The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to fluazifop-P-butyl.

The following summarises the outcome of the evaluation of the newly submitted studies. For information about the studies submitted prior to the current evaluation, please refer to the Re-evaluation Decision document RVD2012-05.

Fluazifop-P-butyl/fluazifop-butyl

Fluazifop-butyl is a racemic mixture, which rapidly converts in vivo almost completely into its R-isomer, also known as fluazifop-P-butyl. Fluazifop-P-butyl is metabolized into its acid metabolite (fluazifop acid) and further into metabolites of which the metabolite Compound 10 was a major metabolite in soil, but minor in rats (Appendix 1, Table 1). For the purposes of the risk assessment, fluazifop-butyl, fluazifop-P-butyl and fluazifop acid were considered to be toxicologically equivalent.

Fluazifop-P-butyl Technical was considered to be of low acute toxicity by the oral and dermal routes in rats and rabbits respectively.

In a toxicokinetic study, a single low dose of ^{14}C-phenyl-fluazifop-butyl (both sexes) or a high dose of ^{14}C-phenyl- or ^{14}C-pyridine-fluazifop-butyl (females only) was administered to mice via gavage. From urine excretion data and residual radioactivity in the carcass, absorption was estimated to be ≥ 38/59% of the administered dose in males and females respectively. Seven days post-administration, the radiolabel concentration was low in the blood stream and organs of metabolism. The highest concentrations were found in abdominal fat of both sexes. At the low dose, excretion was rapid for mice of either sex with ≥ 79% of the administered dose excreted 48 hours after dosing. Male mice excreted less in the urine and more of the administered dose in feces, compared to females. At the high dose, only female mice were dosed and showed decreased excretion in both urine and feces 48 hours post-dosing with the phenyl-labelled fluazifop-butyl. Excretion via the urine was similar with the pyridine-labelled fluazifop-butyl, but even more decreased via feces. Recoveries of radiolabel for the 7-day period in male and female mice were virtually complete. The parent compound was completely metabolized in both sexes and at both doses. Eight metabolites were found in the urine or feces of both male and female mice with a similar qualitative distribution of metabolites. The taurine conjugate and fluazifop acid were the major metabolites in urine and feces. The metabolite Compound 10 representing < 2% of the pyridine-labelled fluazifop-butyl urinary or fecal extracts was not found in phenyl-labelled fluazifop-butyl urine extracts.

In a subchronic dietary toxicity study in hamsters, fluazifop-P-butyl targeted the following organs: kidneys in both sexes and liver, spleen and testes in males. The results were consistent with other subchronic studies performed in rats and dogs. Kidney weight was increased accompanied by significantly altered urinalysis parameters. Generalized toxicity occurred in

males as decreased body weight, body weight gain, food consumption and food efficiency. The liver weight in male animals was increased along with increased incidences of eosinophilia/loss of glycogen in centrilubular hepatocytes. Male animals were also affected by decreased spleen, epididymides and testes weights with increased incidences of tubular degeneration in the testes. Also consistent with other studies, hematological parameters were affected.

The developmental toxicity of fluazifop-P-butyl was evaluated based on the evaluation of two new developmental toxicity studies in rats and the re-evaluation of the three-generation reproductive toxicity study in rats which contained a developmental toxicity portion. In the developmental toxicity studies in rats, minor variations were observed and included increased incidences of delayed ossification and increased manus and/or pes scores. These signs of fetotoxicity occurred in the absence of maternal toxicity, thus providing evidence of sensitivity of the young. At the maternal lowest observed adverse effect level (LOAEL), the dams showed lower body weight gains, decreased food consumption and food efficiency. In the three-generation reproductive toxicity study, malformations were observed in pups including diaphragmatic hernia, microphthalmia and lens abnormalities, in the presence of maternal toxicity.

Compound 10

In a metabolism study in rats, a single low dose of ^{14}C-pyridine-Compound 10 was completely absorbed from the gastrointestinal tract and excreted via urine within 24 hours, mostly as parent compound. Radiolabelled Compound 10 was not retained in the carcass. Compound 10 was of low acute oral toxicity in the rat. In a 28-day dietary rat toxicity study, Compound 10 did not cause adverse effects up to the highest dose tested (176 mg/kg bw/day which was considered an adequate dose in relation to fluazifop-P-butyl toxicity). In a developmental toxicity study in rats, a developmental no observed adverse effect level (NOAEL) could not be established as no adverse effects and no treatment-related malformations or variations were observed up to the highest dose tested (200 mg/kg bw/day), while at this dose, the dams presented lower body weight gains. There was no evidence of sensitivity of the young following exposure to Compound 10. The mutagenicity testing results in the reverse gene mutation assay (Ames) were positive at high doses with and without metabolic activation, while in vitro clastogenicity, micronucleus assay and unscheduled DNA synthesis (UDS) assays were negative. Overall, there was weak evidence of genotoxicity.

Considering the available information, it was concluded that Compound 10 was not of greater toxicity than the parent compound.

The code and chemical names for fluazifop-P-butyl isomers and metabolites can be found in Appendix I, Table 1. Results of the toxicology studies conducted on laboratory animals with fluazifop-P-butyl are summarized in Appendix I, Table 2. The toxicology endpoints for use in the human health risk assessment are summarized in Appendix I, Table 3.

Incident Reports

Since April 26, 2007, registrants are required by law to report incidents, including adverse effects to health and the environment, to the PMRA. As of August 13, 2015, the Incident Reporting Program has received four human and six domestic animal incidents for fluazifop-P-butyl. Most of these incidents occurred in the United States. There were two human incidents that occurred in Canada. In both of these cases, the symptoms were minor and occurred when the product was accidentally splashed.

The incidents did not have an impact on the risk assessment.

PCPA Hazard Characterization

For assessing risks from potential residues in food or from products used in or around residential areas or schools, the *Pest Control Products Act* (PCPA) requires the application of an additional 10-fold factor to threshold effects. This factor should take into account potential pre- and post-natal toxicity and completeness of the data with respect to the exposure of, and toxicity to, infants and children. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, the database contained the standard complement of required studies including four developmental toxicity studies in rats and one in rabbits and a reproductive toxicity study in rats.

With respect to concerns relevant to the assessment of risk to infants and children, sensitivity of the young was not observed in the rabbit developmental toxicity study using fluazifop-butyl, but was observed in the rat developmental toxicity studies using either fluazifop-butyl or fluazifop-P-butyl. Minor variations (ossification delays) were observed in the fetuses in the absence of maternal toxicity. In previously submitted studies using fluazifop-butyl, malformations were observed in the developmental toxicity portion of a three-generation reproductive toxicity study in the rat (diaphragmatic hernia, microphthalmia and lens abnormalities) as well as in two other developmental toxicity studies in the rat (diaphragmatic hernia). At the time of the previous review, additional data were presented to clearly establish the NOAELs for the observed developmental toxicity. These malformations represented serious effects and were observed in the presence and absence of maternal toxicity in different studies.

Overall, the database is adequate for determining the sensitivity of the young. Sensitivity was observed in rat developmental toxicity studies and developmental toxicity was observed in the rat in multiple studies. The PCPA factor was reduced to 3-fold when the NOAEL for developmental toxicity from the three-generation rat reproductive toxicity study was used for risk assessment. Selection of this endpoint provided protection to the sensitivity of the young observed in the developmental toxicity studies in the rat. For all other exposure scenarios, the PCPA factor was reduced to 1-fold.

Acute reference dose (ARfD) for general population, excluding females 13-49 years of age

No acute endpoints of concern for the general population were identified in the toxicology database; therefore, an ARfD was not established.

Acute reference dose (ARfD) for females 13-49 years of age

To estimate risk of acute exposure in females 13-49 years of age, a NOAEL of 7.1 mg/kg bw/day from the three-generation reproductive toxicity study using fluazifop-butyl was selected for risk assessment. At the LOAEL of 17.5 mg/kg bw/day, increased malformations of the eye in F1B litters, namely microphthalmia and lens abnormalities, were observed. This represents the lowest NOAEL for malformations in the database. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the PCPA Hazard Characterization section, the PCPA factor was reduced to 3-fold when using this endpoint in assessing females of reproductive age. The composite assessment factor (CAF) is thus 300.

The ARfD for females 13-49 years of age is calculated according to the following formula:

$$ARfD_{\text{females 13-49 years}} = \frac{NOAEL}{CAF} = \frac{7.1 \text{ mg/kg bw/day}}{300} = 0.02 \text{ mg/kg bw/day of fluazifop-butyl}$$

As fluazifop-butyl, fluazifop-P-butyl and fluazifop acid were considered to be toxicologically equivalent, this ARfD applies to all forms of fluazifop. This ARfD provides a margin of 2500 to the NOAEL established for developmental toxicity in the rat developmental toxicity studies.

Acceptable Daily Intake (ADI)

To estimate risk of repeated dietary exposure, a NOAEL of 0.51 mg/kg bw/day from the combined dietary chronic toxicity/carcinogenicity study in rats using fluazifop-butyl was selected for risk assessment. At the LOAEL of 4.15 mg/kg bw/day, increased mortality, nephropathy and significant changes in hematology parameters were observed. This study provides the lowest NOAEL in the database. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the PCPA Hazard Characterization section, the PCPA factor was reduced to 1-fold. The composite assessment factor (CAF) is thus 100.

The ADI is calculated according to the following formula:

$$ADI = \frac{NOAEL}{CAF} = \frac{0.51 \text{ mg/kg bw/day}}{100} = 0.005 \text{ mg/kg bw/day of fluazifop-butyl}$$

As fluazifop-butyl, fluazifop-P-butyl and fluazifop acid were considered to be toxicologically equivalent, this ADI applies to all forms of fluazifop. This ADI provides a margin of 1420 to the NOAEL for malformations established in the three-generation reproductive toxicity study in rats, and a margin of 400 to the NOAEL at which sensitivity of the young was observed in the developmental toxicity studies in the rat.

Food Residues Exposure Assessment

New residue data for fluazifop-P-butyl in sweet potato and citrus crops, and a processing study for citrus fruits, were submitted and reviewed 1) to revise the MRL on imported sweet potato roots and 2) to establish MRLs on imported citrus fruits and processed commodities. Fluazifop-P-butyl was applied to sweet potato and citrus crops at the GAP of the exporting country (United States), and harvested according to label directions.

Maximum Residue Limit (MRL)

The recommendation for MRLs for fluazifop-butyl was based upon the submitted field trial data in the exporting country, and the guidance provided in the OECD MRL Calculator. MRLs to cover residues of fluazifop-butyl in/on crops and processed commodities are proposed as shown in Table 1. Residues in processed commodities not listed in Table 1 are covered under the proposed MRLs for the raw agricultural commodities (RACs).

TABLE 1 Summary of Field Trial and Processing Data Used to Support Maximum Residue Limit(s) (MRLs)

Commodity	Application Method/Total Application Rate (g a.i./ha)	PHI (days)	Residues (ppm)		Processing Factors	Currently Established MRL (ppm)	Recommended MRL (ppm)
			LAFT [1]	HAFT [2]			
Sweet potato roots	825 - 862	12 - 16	0.112	0.882	-	0.5	1.5
Citrus Crops (Crop Group 10)							
Lemon, orange and grapefruit (US trials of 1986)	680 - 2520	14	<0.03	<0.03	5X (citrus oil) 0.5X (orange juice)	none	0.03 for all crops in the crop group (CG 10) 0.15 for citrus oil
Orange and grapefruit (US trials of 2000)	1232 - 1288	12 - 14	<0.01	<0.01		none	

[1]LAFT = lowest average field trial
[2]HAFT = highest average field trial

Following the review of all available data, MRLs as proposed in Table 1 are recommended to cover the residues of fluazifop-butyl. Based on an updated acute basic dietary risk assessment conducted using a new acute reference dose of 0.02 mg/kg bw, and the updated chronic dietary exposure risk assessment for fluazifop-P-butyl, residues in the requested imported crop commodities at the recommended MRLs will not pose an unacceptable risk to any segment of the population, including infants, children, adults and seniors.

Conclusion

The PMRA has completed a review of the information available for Fluazifop-P-butyl Technical and determined the information sufficient to support an MRL on imported sweet potato roots at 1.5 ppm and to establish MRLs on imported citrus crops and processed commodities as listed above in Table 1.

List of Abbreviations

♂, ♀	male, female
<	less than
>	greater than
≥	greater than or equal to
µg	microgram(s)
abs	absolute
AD	administered dose
ADI	acceptable daily intake
a.i.	active ingredient
Alpk	Alderley Park (Wistar derived rat strain)
ARfD	acute reference dose
bw	body weight
bwg	body weight gain
CAF	composite assessment factor
^{14}C-	radiocarbon labelling
DNA	deoxyribonucleic acid
F1B	second litter from first generation
FB	fluazifop-butyl
fc	food consumption
fe	food efficiency
FPB	fluazifop-P-butyl
g	gram(s)
GAP	Good Agricultural Practice
GD	gestation day
ha	hectare(s)
HAFT	highest average field trial
HD	high dose
HDT	highest dose tested
kg	kilogram(s)
LAFT	lowest average field trial
LD	low dose
LD_{50}	lethal dose to 50%
LOAEL	lowest observed adverse effect level
mg	milligram(s)
MOE	margin of exposure
MRL	maximum residue limit
NOAEL	no observed adverse effect level
NZW	New Zealand white
PCPA	Pest Control Product Act
PMRA	Pest Management Regulatory Agency
ppm	part(s) per million
RAC	raw agricultural commodity
RVD	Re-evaluation Decision Document

SPF	specific pathogen free
UDS	unscheduled DNA synthesis
US	United States
wt	weight

Appendix I Tables and Figures

Table 1 Chemical Names of Isomers and Metabolites of Fluazifop-butyl

Code/Trivial name	Chemical name
FB/Fluazifop-butyl	(RS)2-(4-[5-(trifluoromethyl-2-pyridinyloxy]phenoxy)propionic acid)
FPB/Fluazifop-P-butyl	(2R)-2-[4-[[5-(trifluoromethyl)-2-pyridinyl]oxy]phenoxy]propanoate
Fluazifop acid	(R)-2-{4-[5-(trifluoromethyl)-2-pyridyloxy]phenoxy}propionic acid
R118106/Compound 3	(RS)-2-(4-hydroxyphenoxy)propanoic acid
R154719/Compound 10	5-(trifluoromethyl)-2(1H)-pyridinone

Table 2 Toxicity Profile of Fluazifop-P-butyl Technical Herbicide

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted). Effects seen above the LOAEL(s) have not been reported in this table for most studies for reasons of brevity.

Study Type/Animal/PMRA #	Study Results
Acute Oral Toxicity SPF Rats PMRA 1230390	$LD_{50♂}$ = 3680 mg/kg bw $LD_{50♀}$ = 2451 mg/kg bw **Low Toxicity**
Acute Dermal Toxicity NZW Rabbits PMRA 1230390	LD_{50} > 2111 mg/kg bw **Low Toxicity**
90-Day oral toxicity (diet) Golden Syrian Hamsters PMRA 2361805	NOAEL= 78/79 mg/kg bw/day in ♂/♀ LOAEL = 292/320 mg/kg bw/day in ♂/♀; effects included increased kidney wt, decreased hematology and clinical chemistry and urinalysis parameters; decreased bw and bwg, decreased fc & fe, increased liver wt, increased incidences of eosinophilia/loss of glycogen in centrilubular hepatocytes, decreased abs testes wt & epididymides wt, increased incidence of testes tubular degeneration, decreased spleen wt (♂)

Study Type/Animal/PMRA #	Study Results
Developmental Toxicity Study in Rats Wistar Rats PMRA 2361808	Maternal NOAEL = 100 mg/kg bw/day Maternal LOAEL not established Developmental NOAEL = 2 mg/kg bw/day Developmental LOAEL = 5 mg/kg bw/day; effects included increased 5th sternebrae bipartite & partially ossified, calcaneum not ossified, increased partial ossification of parietals, increased manus score **Evidence of sensitivity of the young**
Developmental Toxicity Study in Rats Wistar Rats PMRA 2361809	Maternal NOAEL = 20 mg/kg bw/day Maternal LOAEL = 300 mg/kg bw/day; effects included decreased bwg (GD 7-16), decreased fc & fe Developmental NOAEL = 1.0 mg/kg bw/day Developmental LOAEL = 20 mg/kg bw/day; effects included delayed ossification (occipital, parietals), no ossification (cervical centra, calcaneum), increased manus and pes scores **Evidence of sensitivity of the young**
Developmental/Reproductive Toxicity Studies for Fluazifop-butyl (FB)	
Three-generation reproductive dietary study Wistar rats PMRA 1220150 and 1220151	Parental toxicity NOAEL = 0.74/0.88 mg/kg bw/day in ♂/♀ LOAEL = 5.8/7.1 mg/kg bw/day in ♂/♀; effects included: decreased bwg and spleen and kidney toxicity at the next dose Offspring toxicity NOAEL = 0.74/0.88 mg/kg bw/day in ♂/♀ LOAEL = 5.8/7.1 mg/kg bw/day in ♂/♀; effects included: increased incidences of hydronephrosis, decreased bwg during lactation Reproductive toxicity: NOAEL = 21.7/17.5 mg/kg bw/day in ♂/♀ LOAEL Not established Developmental toxicity: NOAEL = 5.8/7.1 mg/kg bw/day in ♂/♀ LOAEL = 21.7/17.5 mg/kg bw/day in ♂/♀; effects included: decreased fetal and placental weights, increased number of small fetuses, increased incidences of microphthalmia and lens abnormalities, decreased degree of ossification and skeletal variations **No evidence of sensitivity of the young**

Study Type/Animal/PMRA #	Study Results
Toxicokinetics	
Toxicokinetics with Fluazipfop-butyl (FB)	
Absorption, excretion and tissue retention with FB (Supplemental study) Alderley Park Mice PMRA 2361815	^{14}C-phenyl-FB (≥99.5% a.i.) or ^{14}C-pyridine-FB (98% a.i.) was administered to SPF Alpk mice in a single oral dose by gavage at the low dose (LD) level of 1 mg/kg bw (phenyl label; 3/sex; groups A and B) or at the high dose (HD) level of 150 mg/kg bw (phenyl or pyridine label; 6 females/group; groups C and D). **Absorption:** From urine excretion data and residual radioactivity in the carcass, absorption was estimated to be ≥ 38/59% of administered dose (AD) in males and females, respectively. **Distribution:** Seven days post-administration, concentrations of radioactivity in the blood of male mice were low (< 0.01 µg/g) and were only marginally higher for females (0.02 µg/g). Low concentrations of radioactivity were also found in the liver (0.02 µg/g in both sexes) and kidneys (0.05 and 0.09 µg/g in males and females, respectively). The radioactivity was highest in the abdominal fat of both sexes (0.93 and 1.39 µg/g, males and females, respectively). **Excretion:** At the LD, excretion was rapid for mice of either sex with ≥ 79% of the AD excreted 48 hours after dosing. Male mice excreted ~28% of the AD in urine and ~52% of the AD in feces compared to 46% in urine and ~33% in feces for females. Recoveries for the 7-day period in male and female mice were ~98% and ~95% of the AD. At the HD, excreta were collected for 48 hours after dosing. Female mice dosed with phenyl-labelled FB excreted 17.3% and 26.3% of the AD in urine and feces, respectively, whereas female mice dosed with pyridine-labelled FB excreted 13.3% and 12.2% of the AD in urine and feces, respectively. **Metabolism:** The parent compound was completely metabolized in both sexes and at both doses (only females were tested at the high dose). Eight metabolites were found in the urine of both male and female mice given the LD of phenyl-labelled FB and the qualitative distribution of metabolites was similar. The taurine conjugate and FB acid were the major metabolites in urine with a proportion (of all metabolites) of 80.2/14.4% and 61.4/27.7% in male and female mice, respectively. Eight metabolites were also found in the extracts of urine from female mice dosed with the phenyl- or pyridine-labelled FB at the HD and the qualitative distribution of metabolites was similar to that obtained with male and female animals dosed at the LD. The taurine conjugate and FB acid were the major metabolites in urine with a proportion of 42.4/48.0% and 23.6/55.9% with the phenyl- and pyridine-labelled compound, respectively. The metabolite 5-(trifluoromethyl)-2-pyridinone representing 1.1% of the pyridine-labelled FB urinary extracts was not found in phenyl-labelled FB urine extracts. The qualitative distribution of metabolites in fecal extracts from mice dosed with phenyl-labelled FB at the LD and HD was similar and the same metabolites accounted for most of the radioactivity. Eight metabolites were found in feces from male and female mice given a LD of phenyl-labelled FB. The taurine conjugate metabolite accounted for 45.9% and 33.3% and FB acid metabolite accounted for 46.3% and 47.0% in male and female mice, respectively. Female mice given a single oral HD of phenyl-labelled FB showed a similar qualitative and quantitative distribution of metabolites to that obtained in fecal extracts from LD female mice. Fecal extracts from mice dosed with pyridine-labelled FB at the HD contained slightly more (1.6%) 5-(trifluoromethyl)-2-pyridinone than did the extract of urine. The qualitative distribution of metabolites was otherwise similar to that obtained with the other fecal extracts although some quantitative differences were observed. When hydrolysis products of FB acid and its taurine conjugate were hydrolyzed, more than 90% of the conjugate was hydrolysed to FB acid. Some hydrolysis of both the taurine conjugate and FB acid to 2-(4-hydroxyphenoxy)propionic acid (metabolite 3) also occurred.

Study Type/Animal/PMRA #	Study Results
Toxicokinetics with plant metabolite R154719	
Absorption: Single oral dose with R154719 (Supplemental study) Wistar Rats PMRA 2361814	Pyridine-2,6-^{14}C-R154719 (97.7% a.i.) was administered to 4 male-bile duct cannulated rats in single dose by gavage at dose levels of 0, 0.5 mg/kg bw. The purpose of this supplemental study was to determine the extent of absorption of R154719 from the gastrointestinal tract into the systemic circulation based on biliary and urinary excretion and the residual radioactivity in the carcass, to determine the rates and routes of excretion of R154719 and/or its radiolabeled metabolites, and to investigate the quantitative metabolite profile in urine and bile fluid. Pyridine-labeled R154719 was completely absorbed from the gastrointestinal tract (97% of the AD). The test compound was excreted via urine (~84% of AD) and bile (~9% of AD) within 24 hours while only 0.4% of the AD was excreted in the feces. At this time-point in urine, unchanged R154719 at 73.2% of AD was the major fraction recovered while it represented a minor fraction in bile at 1.5% of the AD. A major fraction in bile was not identified and represented 6.6% of the AD. The carcass retained only 0.4% of the AD after 48 hours.
Acute Toxicity Studies with plant metabolite R1514719	
Acute Oral toxicity SPF Rats PMRA 2361803	$LD_{50♂}$ = 3866 mg/kg bw $LD_{50♀}$ = 3417 mg/kg bw **Low toxicity**
Short-Term Toxicity Studies with plant metabolite R154719	
28-day Dietary Toxicity Study Wistar Rats PMRA 2361806	NOAEL = 176 mg/kg bw/day in ♂/♀ (HDT) LOAEL = Not established; No effects at the high dose.
Developmental/Reproductive Toxicity Studies with plant metabolite R154719	

Study Type/Animal/PMRA #	Study Results
Developmental Toxicity Study, range-finding (Supplemental) Sprague-Dawley Rats PMRA 2414215	NOAEL/LOAEL not established as the study was considered to be supplemental **Preliminary phase** **Maternal effects included: At ≥ 500 mg/kg bw/day:** unsteady gait, decreased activity, slow breathing, partially closed eyes; **At 750 mg/kg bw/day:** Sacrificed on GD 3 (preceded by slow breathing, prostration, cold body surface, unsteady gait and decreased activity; bw loss GD 1-3 at 750 mg/kg bw/day only) Developmental effects were not assessed. **Main study** **Maternal effects included: At ≥ 200 mg/kg bw/day:** Decreased activity, piloerection, unsteady gait and slow breathing, pale feces, bw loss and decreased bwg; **At ≥ 400 mg/kg bw/day:** Partially closed eyes, prostration, decreased fc, decreased total implantations, decreased live fetuses, increased post-implantation loss, decreased gravid uterine wt; **At 600 mg/kg bw/day:** Terminated early on GD 6 or 8 due to a decline in clinical condition (partially closed eyes, piloerection, prostration, decreased activity, slow breathing, and unsteady gait) and decreased bw **Developmental effects included: At ≥ 200 mg/kg bw/day:** decreased fetal wt; **At 400 mg/kg bw/day:** decreased total implantations, decreased live fetuses, increased post-implantation loss, decreased litter wt
Developmental Toxicity Study Sprague-Dawley Rats PMRA 2361807	Maternal NOAEL = 60 mg/kg bw Maternal LOAEL = 200 mg/kg bw; effects included: Decreased bwg (GD 6-14) Developmental NOAEL = 200 mg/kg bw/day Developmental LOAEL = Not established: No treatment-related malformations or variations at any dose level. No evidence of developmental toxicity. **No evidence of sensitivity of the young**
Genotoxicity Studies with plant metabolite R154719	
Reverse gene mutation assay (Ames test) S. typhimurium strains (TA1535, TA1537, TA1538, TA98 and TA100) PMRA 2361810	**Positive** result with or without activation in TA1535 (≥ 1000 µg/plate) and TA100 (5000 µg/plate). Base-pair substitutions.

Study Type/Animal/PMRA #	Study Results
In vitro mammalian clastogenicity Human lymphocytes PMRA 2361812	**Negative**
In vivo micronucleus test C57BL/6J mice PMRA 2361813	**Negative** There were slight but statistically significant increases in the frequency of micronucleated polychromatic erythrocytes at 72 hours in males and females. Such increases were not observed at 24 or 48 hours. It was concluded that R154719 did not cause a biologically significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow.
Unscheduled DNA Synthesis test Rat hepatocytes PMRA 2361811	**Negative**

Table 3 Toxicology Endpoints for Use in Health Risk Assessment for Fluazifop-P-butyl

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary general population excluding females 13-49 years of age	No acute endpoints were identified.		
Acute dietary females 13-49 years of age	Three-generation rat reproductive study (developmental toxicity portion)	NOAEL= 7.1 mg/kg bw/day Increased incidence of malformations of the eye in F1B litters, microphthalmia and lens abnormalities	300
	$ARfD_{females\ 13\text{-}49\ years\ of\ age}$ = 0.02 mg/kg bw		
Repeated dietary	2-year rat chronic rat toxicity study	NOAEL= 0.51 mg/kg bw/day Increased mortality, nephropathy and hematology parameters	100

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
	ADI= 0.005 mg/kg bw/day		
Dermal and inhalation[2] occupational scenarios (all durations)	Three-generation rat reproductive study (developmental toxicity portion)	NOAEL= 7.1 mg/kg bw/day Increased incidence of malformations of the eye in F1B litters, microphthalmia and lens abnormalities	300

[1] CAF (composite assessment factor) refers to a total of uncertainty and PCPA factors for dietary assessments; MOE refers to a target MOE for occupational and residential assessments

[2] For inhalation scenarios, when an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

References

PMRA Document Number	Reference
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2361845	2013, Storage of fluazifop-P-butyl residues as fluazifop acid (fluazifop-P) in processed fraction of potato, soybean, tomato and wheat under freezer storage conditions for up to 12 months. DACO: 7.3.
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