UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: December 10, 2004

MEMORANDUM

SUBJECT: **Fluazifop-P-butyl:** Revised HED Chapter of the Tolerance Reassessment Eligibility Document (TRED). PC Code: 122809, Case # 2285, DP Barcode: D291903

Regulatory Action: Tolerance Reassessment, Phase 3 of the Interim Public Participation Process
Risk Assessment Type: Single Chemical Aggregate

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1.0 Executive Summary

This assessment provides information to support the issuance of a risk management decision document known as a Tolerance Reassessment Eligibility Decision (TRED) Document for fluazifop-P-butyl. EPA's pesticide reregistration process provides for the review of older pesticides (those initially registered prior to November 1984) under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) to ensure that they meet current scientific and regulatory standards. The process considers the human health and ecological effects of pesticides and incorporates a reassessment of tolerances (pesticide residue limits in food) to ensure that they meet the safety standard established by the Food Quality Protection Act (FQPA) of 1996.

Fluazifop-P-butyl [(*R*)-2-(4-((5-(trifluoromethyl)-2-pyridinyl)oxy)phenoxy) propanoic acid, butyl ester] is a selective herbicide registered for use for postemergence control of perennial and annual grass weeds. Fluazifop-P-butyl accumulates in the actively growing regions of the plant (meristems of roots and shoots, root rhizomes and stolons of grass), where it interferes with energy [adenosine triphosphate (ATP)] production and cell metabolism in susceptible species. Fluazifop-P-butyl is currently registered for food/feed use on asparagus, carrot, coffee, cotton, endive (escarole), garlic, macadamia nut, onion, pecan, pepper, rhubarb, soybeans, stone fruits, sweet potato, and yam, as well as registered for use on lawns/turf.

Fluazifop-P-butyl is the resolved isomer ® enantiomer) of fluazifop-butyl [(*R,S*)-2-(4-((5-(trifluoromethyl)-2-pyridinyl)oxy)phenoxy)propanoic acid, butyl ester]. The fluazifop-butyl isomers are List B chemicals. Fluazifop-butyl (PC code 122805) has been canceled and only fluazifop-P-butyl is being supported for reregistration.

Fluazifop-butyl and fluazifop-P-butyl have low acute toxicity by the oral, dermal and inhalation routes, are mildly irritating to the eye and skin, and are not skin sensitizers. Subchronic and chronic toxicity studies with fluazifop-butyl or fluazifop-P-butyl show that the rat is more sensitive to toxic effects than the dog, rabbit or hamster, possibly due to longer retention time of the major metabolite (fluazifop acid) in the rat. The kidney and liver are the target organs and the toxicity is expressed as exacerbation of age related kidney toxicity and liver toxicity in the presence of peroxasome proliferation. An acute dietary endpoint for females 13-49 years of age was selected from a developmental toxicity study in rats, based on diaphragmatic hernia. No appropriate endpoint attributable to a single dose was identified for the general U.S. population. The short-term incidental oral endpoint was selected from the developmental toxicity studies in rats and is based on maternal body weight gain decrement. The chronic dietary (all populations), intermediate-term dermal and inhalation, and intermediate-term incidental oral endpoints were selected from the 2-generation reproduction study in rats based on decreased spleen, testes and epididymal weights in males, and decreased uterine and pituitary weights in females. The short-term dermal and inhalation endpoints used in the assessment were selected from the developmental toxicity studies in rats based on decreased fetal weights, hydroureter and delayed ossification. Though this endpoint was selected by the assessment team specifically for females 13-49 years of age, and a separate, higher, dose/endpoint was selected for all other population subgroups from the developmental toxicity studies in rats, based on maternal weight gain decrement, the fluazifop-P-butyl assessment team chose to use the female-specific endpoint for all population subgroups. This approach was taken

because by using the lower dose/endpoint for all population subgroups, the risk assessment is protective of any toxic effects seen at higher doses. This approach is particularly appropriate as a first cut or screening level assessment to determine if there are any potential risks of concern. Since oral NOAELs were selected for dermal endpoints, dermal absorption factors, calculated from a dermal absorption and pharmacokinetic study in humans, of 2% for high exposures and 9% for low exposures were used for route-to-route extrapolation. Fluazifop-P-butyl is classified as "not likely to be carcinogenic to humans" and no mutagenic potential was observed in adequate *in vivo* and *in vitro* studies with fluazifop-butyl and fluazifop-P-butyl.

Though increased susceptibility of offspring was observed in rats, the degree of concern is low based on the following considerations: the endpoint of concern (delayed ossifications) is considered to be a developmental delay as opposed to a malformation or variation which is considered to be more serious in nature; there were considerable variations in the incidences among the five rat developmental toxicity studies; the NOAELs/LOAELs for this effect were well defined and consistent across these studies; and a developmental endpoint of concern for a single dose effect (diaphragmatic hernia) is used for assessing acute dietary risk. Therefore, there is no residual uncertainty for pre and/or post natal toxicity. The Assessment team concluded that there was not a concern for neurotoxicity resulting from exposure to fluazifop-P-butyl at relevant exposure levels. There was no evidence of clinical signs indicative of neurotoxicity or neuropathology in the available studies. Marginal increases in brain weights at termination were seen in a subchronic toxicity study in rats and a carcinogenicity study in hamsters, but only at high doses. The Assessment team concluded that there is not a concern for developmental neurotoxicity resulting from exposure to fluazifop-butyl or fluazifop-P-butyl. The FQPA factor was reduced to 1X and no database uncertainty factors are needed for any database deficiencies.

Conservative acute and chronic dietary exposure analyses (food + water) were performed in order to determine the exposure and risks resulting from the registered uses of fluazifop-P-butyl. Tolerance level values with a ratio adjustment for additional metabolites of concern, default processing factors, and screening level point estimate for residues in water were used in these assessments. No percent crop treated (%CT) refinements were included for the acute dietary exposure analysis; however, %CT refinements were used for the chronic analysis. Acute dietary risk estimates are provided for the population subgroup of females 13-49 years of age (< 2% aPAD) and conclude that for all supported commodities, the acute dietary risk estimates are below the Agency's level of concern (100% aPAD) at the 95th exposure percentile. Chronic dietary risk estimates were calculated for the U.S. population (total) and various population subgroups. The chronic assessment concludes that for all supported commodities, the chronic dietary risk estimates are below the Agency's level of concern (100 % cPAD) for the U.S. population (30% cPAD) and all population subgroups. The most highly exposed population subgroup in the chronic dietary exposure analysis is all infants less than 1 year of age (95% cPAD). The most significant contribution (dietary "drivers") to the risk estimate are water, carrot babyfood, and spinach babyfood.

Exposures and risks for residential handlers were assessed using the revised draft Standard Operating Procedures (SOPs) for Residential Exposure Assessment and the 2001 Recommended Revisions by the Science Advisory Council for Exposure (Policy #12). Exposures were estimated using surrogate unit exposure values from the Outdoor Residential

Exposure Task Force (ORETF). Since ORETF does not include data for scenarios using ready-to-use spray bottle application, data from a proprietary study were used to estimate those exposures (MRID# 447393-01). Estimated residential handler risks, calculated as Margins of Exposure (MOEs) are greater than HED's level of concern (LOC = 100) for all of the scenarios assessed and therefore, are not of concern.

Short-term postapplication exposures may occur following applications at residential sites. Residential exposures were also estimated based on HED's 1997 draft SOPs for Residential Exposure Assessments and the 2001 Recommended Revisions by the Science Advisory Council for Exposure (Policy #12). Short-term risks (MOEs) estimated for postapplication exposure are greater than HED's LOC for all of the assessed scenarios and are not of concern.

High-contact dermal postapplication exposures for toddlers to fluazifop-P-butyl on treated lawns have been combined with incidental oral postapplication exposures for toddlers, as these events are likely to coincide. The MOEs for the combined short-term postapplication risks to toddlers are greater than HED's LOC for all of the assessed scenarios and are not of concern.

Acute, chronic and short-term aggregate risk assessments were performed using high-end exposures, the most conservative endpoints, and worst-case assumptions concerning potential concurrent exposure scenarios. Taking into account the supported uses proposed in this action, HED can conclude with reasonable certainty that combined residues of fluazifop-P-butyl from all sources would not likely result in an aggregate risk of concern for any population subgroup.

2.0 Ingredient Profile

2.1 Summary of Registered/Proposed Uses

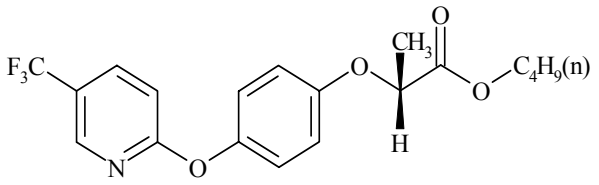
A comprehensive summary of the registered food/feed use patterns of fluazifop-P-butyl can be found in *Fluazifop-P-butyl. Revised TRED - Report on FQPA Tolerance Reassessment Progress and Interim Risk Management Decisions. Residue Chemistry Considerations. Case No. 2285. Sherrie L. Kinard. December 8, 2004*. A tabular summary of the residue chemistry science assessments for reregistration of fluazifop-P-butyl is presented in Table 6 of the Residue Chemistry chapter (12/08/04). The conclusions listed in Table 6 regarding the reregistration eligibility of fluazifop-P-butyl food/feed uses are based on the use patterns supported by the registrant, Syngenta Crop Protection, Inc. When end-use product DCIs are developed, the Registration Division (RD) should require that all end-use product labels (e.g., MAI labels, SLNs, and products subject to the generic data exemption) be amended such that they are consistent with the primary registrant's labels.

Fluazifop-P-butyl [(*R*)-2-(4-((5-(trifluoromethyl)-2-pyridinyl)oxy)phenoxy)propanoic acid, butyl ester] is a selective herbicide registered for use to provide postemergence control of perennial and annual grass weeds. Fluazifop-P-butyl is currently registered for food/feed use on asparagus, carrot, coffee, cotton, endive (escarole), garlic, macadamia nut, onion, pecan, pepper, rhubarb, soybean, stone fruits, sweet potato, and yam. Fluazifop-P-butyl products are registered in the U.S. to Syngenta Crop Protection, Inc. under the trade names Fusilade®, Fusion®,

Oramec®, Tornado®, and Typhoon®. Currently, the 0.086, 0.47, 1, 2, and 4 lb/gal emulsifiable concentrate (EC) formulations of fluazifop-P-butyl are registered for use on food/feed crops. The products are typically applied as postemergence foliar or soil applications using ground or aerial equipment; preplant, at-planting and/or postharvest applications (to the plant) are also registered for some crops.

2.2 Structure and Nomenclature

The purified fluazifop-P-butyl [R] isomer is supported for reregistration and the previously registered fluazifop-butyl [RS] isomeric mixture is not supported for reregistration.

TABLE 2.2. Test Compound Nomenclature	
Chemical structure	
Empirical Formula	$C_{19}H_{20}F_3NO_4$
Common name	Fluazifop-P-butyl
Company trade names	Fusilade, Fusion, Oramec, Tornado, Typhoon
IUPAC name	butyl (2*R*)-2-(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}phenoxy)propanoate
CAS name	(*R*)- 2-(4-((5-(trifluoromethyl)-2-pyridinyl)oxy)phenoxy)propanoic acid, butyl ester
CAS #	79241-46-6
Chemical Class	Aryloxyphenoxy Propionate
Known Impurities of Concern	Potential for the formation of halogenated dibenzo-p-dioxins, halogented dibenzofurans or N-nitrosamines is not envisioned at any stage." MRID# 92068001

2.3 Physical and Chemical Properties

Based on measured, or estimated physical/chemical (PChem) properties, fluazifop-P-butyl is not volatile, though inhalation exposures can occur as a result of some application methods (occupational and non-occupational). Fluazifop-P-butyl is also not expected to be readily absorbed by the dermal route, based on its PChem properties, and this is borne out in the submitted human dermal absorption and pharmacokinetic studies (2-9% absorption).

TABLE 2.3 Physicochemical Properties		
Parameter	Value	Reference
Molecular Weight	383.37	MRID# 92067999
Melting point/range	5° C	"
pH	6.2	MRID# 46180701C
Density	1.20g.cm^{-3}	MRID# 92067999
Water solubility (20° C)	1 mg/L	"

TABLE 2.3 Physicochemical Properties		
Parameter	Value	Reference
Solvent solubility (temperature not specified)	Soluble in most organic solvents >500 g/L in acetone, dichloromethane, ethyl acetate, hexane, methanol, toluene, and xylene	"
Vapor pressure (25 C)	3 x 10^{-8} kPa at 20° C	"
Dissociation constant, pKa	- 3.1 (estimated)	"
Octanol/water partition coefficient, log P_{OW}	4.5 at 20° C	"
UV/visible absorption spectrum	Maximum at 225 and 272	MRID# 46180701C

3.0 Metabolism Assessment

3.1 Comparative Metabolic Profile

The submitted metabolism data on fluazifop-butyl and fluazifop-P-butyl (the subject of reregistration) support the finding that they are similar, if not identical in toxicity. Rat metabolism data showed that [RS] fluazifop-butyl is converted to [R] fluazifop acid within a short time period. Fluazifop-butyl is rapidly hydrolyzed to fluazifop acid by blood esterases and the [S] enantiomer is rapidly converted to the [R] enantiomer; apparently the [R] enantiomer is the preferred configuration. Whether rats are administered [RS] fluazifop-butyl (50:50 mixture) or [R] fluazifop-P-butyl (purified, 90%:10%= [R]:[S]), a ratio of [R]:[S]= 97%:3% for fluazifop acid was identified within a hour in the blood of rats.

Human oral studies with fluazifop-butyl show rapid excretion of fluazifop acid in the urine and almost no excretion in the feces of humans (MRID# 00131464). Additional metabolism studies with fluazifop-butyl, as well as fluazifop-P-butyl suggest individual variation in the rate of excretion is associated with exposure. This individual variation was noted in the rat, dog, and human studies. Male rats were the only sex and species shown to excrete the pesticide in the bile, which resulted in a longer half lives in males. However, variation in half lives or delayed absorption were also noted in humans. This assumes that individual variation in the rate of absorption and excretion may have been at least partly due to experimental variation. In rats, fluazifop acid was the major metabolite excreted in the urine and feces and, essentially the only metabolite along with conjugates excreted in the urine of females. Strong binding of fluazifop acid to plasma proteins was found in rat and human blood with approximately 92% being bound. Typically, in females, 90% of the test material administered is excreted in the urine and about 10% in feces, whereas in males 44% is excreted in urine and about 52% in feces in 7 days. The metabolite fluazifop acid and it's conjugates are the major products excreted in the urine and feces of males and females with typically less than 2.6% being the ether cleavage between the pyridine and phenyl residues. Other metabolic products are less than 3%.

3.2 Nature of the Residue in Foods

3.2.1 Description of Primary Crop Metabolism

The nature of the residue in soybean is understood; however, the nature of the residue is not understood in root and tuber crops or in leafy vegetables. The submitted carrot and celery metabolism studies have been reviewed by HED and determined to be inadequate to satisfy data requirements at this time. New plant metabolism studies with a root/tuber crop (such as carrot or sweet potato) and a leafy vegetable (such as endive or celery) must be submitted.

The submitted plant metabolism data for fluazifop on carrot roots identified the major residue as fluazifop acid (free and conjugated) in both the pyridyl and phenyl labeled roots. In the celery metabolism data, the major residues identified were fluazifop (free and conjugated) and fluazifop acid (free and conjugated), with higher residues in the leaves than in the stems. The metabolites 2-(4-hydroxyphenoxy) propionic acid and 5-trifluoromethyl-2-pyridone were also identified in both the carrot and celery metabolism studies. In the soybean metabolism data, the major residue identified was fluazifop acid (free and conjugated).

Fluazifop (free and conjugated) and fluazifop acid (free and conjugated) are considered to be the residues of concern for tolerance expression in plants; however, for risk assessment purposes, since MARC was unable to conclude that these additional metabolites mentioned above would be significantly less toxic than the parent, the residues of concern in plants are fluazifop (free and conjugated), fluazifop acid (free and conjugated), 2-(4-hydroxyphenoxy) propionic acid, and 5-trifluoromethyl-2-pyridone.

The proposed metabolic profile of fluazifop-P-butyl in celery can be found in Figure 3.3 of *Fluazifop-P-butyl. Report of the Metabolism Assessment Review Committee. PC Code: 122809. DP Barcode: 298939. Sherrie L. Kinard, David Anderson, and William P. Eckel. July 8, 2004.*

3.2.2 Description of Livestock Metabolism

The qualitative nature of the residue in livestock is not understood. New metabolism studies for ruminants and poultry must be submitted. ICI Americas, Inc., now known as Syngenta Crop Protection, Inc., submitted metabolism studies with dairy cattle and laying hens. These studies have been reviewed by HED and determined to be inadequate to satisfy data requirements because the dosing levels were too low to allow complete elucidation of the nature of the residue in livestock.

The submitted livestock metabolism data for fluazifop in meat identified the major residues fluazifop (free and conjugated) in all cow tissues. TLC analysis of the major extract prior to base hydrolysis indicated that the major residue in milk was a triglyceride ester(s) of fluazifop. The metabolite 2-(4-hydroxyphenoxy)-5-trifluoromethyl pyridine was the only other metabolite identified in kidney and in liver.

The submitted livestock metabolism data for fluazifop in poultry identified fluazifop as the major component in all hen matrices in both the pyridyl and phenyl labeled hens. In egg

yolk, the majority of residues identified were the isomeric dipalmityl triglyceride esters of fluazifop. In whole egg, egg yolk, and fat, a large portion of the lipophilic fraction was converted to fluazifop following base hydrolysis. Free fluazifop was also identified in egg yolk.

Fluazifop (free and conjugated) and fluazifop acid (free and conjugated) are considered to be the residues of concern in livestock matrices for both tolerance expression and for risk assessment purposes.

No metabolic pathway was proposed for fluazifop-butyl in poultry; however, the proposed metabolic profile of fluazifop-butyl in meat and milk can be found in Figure 3.5 of *Fluazifop-P-butyl. Report of the Metabolism Assessment Review Committee. PC Code: 122809. DP Barcode: 298939. Sherrie L. Kinard, David Anderson, and William P. Eckel. July 8, 2004.*

3.2.3 Description of Rotational Crop Metabolism, including identification of major metabolites and specific routes of biotransformation

The qualitative nature of the residue in rotational crops is not understood. New confined rotational crop studies must be submitted. The confined rotational crop study has been determined to be inadequate to satisfy data requirements.

Currently, the following plant back interval exists on the product labels for EPA Reg. Nos. 100-994, 100-1003, 100-1059, 100-1069, and 100-1070: a 60-day plant back interval for rotational crops such as corn, sorghum, and cereals. The following plant back intervals exist on the product labels for EPA Reg. Nos. 100-1071 and 100-1116 (MAIs with sodium salt of fomesafen): a 4-month plant back interval for small grains such as wheat, barley, and rye; a 10-month plant back interval for beans, peas, corn, cotton, peanuts, and rice; and an 18-month plant back interval for alfalfa, seed corn, sunflowers, sugar beets, sorghum, or any other crop.

Radioactive residues (expressed as fluazifop-butyl equivalents) were <0.01 ppm in all crops grown to maturity in ^{14}C-phenyl labeled fluazifop-butyl treated soil. Radioactive residues (expressed as fluazifop-butyl equivalents) were also <0.01 ppm in lettuce, wheat grain, and sugar beet root in ^{14}C-pyridyl labeled fluazifop-butyl treated soil; however, in wheat straw and sugar beet foliage, residues were 0.10 ppm and 0.03 ppm respectively.

No metabolic pathway was proposed for fluazifop-butyl in rotational crops.

3.3 Environmental Degradation

Environmental fate studies indicate that fluazifop-P-butyl is not mobile and not persistent. The predominant environmental fate process appears to be microbially-assisted hydrolysis to fluazifop acid and 5-trifluoromethyl-2-pyridone, which are considered to be mobile and therefore, can potentially reach surface and ground waters. Aerobic soil metabolism studies showed that the half-life of the parent ester is on the order of a few hours. The properties of fluazifop acid, namely high mobility and long persistence in water (78-day hydrolysis half-life at pH 7) and anaerobic soil (half-life 1 to 3 years, MRID# 92067033) indicate that it might persist from year to year in the subsurface, and move with flowing ground water. The degradate 5-trifluoromethyl-2-pyridone does not sorb to soil, indicating very high mobility. A minor

degradate is 2-(4-hydroxyphenyl)-5-trifluromethylpyridine. There are no data on its mobility, but it is expected to be similar to that of fluazifop acid.

Volatilization of the parent ester is not likely given its short half-life in soil and low volatility (Henry's law constant about 6.2 E-8 atm•m^3/mol). Volatilization of the acid is also not likely, since it will have a higher solubility and lower vapor pressure than the parent, both of which will reduce the Henry's law constant from the parent's value.

Water softening, in which the alkalinity is raised to pH 10 or 11 by the addition of lime or soda ash, will rapidly degrade the parent fluazifop-P-butyl to fluazifop acid. Precipitation of particulates (coagulation and flocculation) is not expected to remove fluazifop acid or 5-trifluoromethyl-2-pyridone because they are only weakly bound to soil particles.

3.4 Tabular Summary of Metabolites and Degradates

Table 3.4 Tabular Summary of Fluazifop-P-butyl Metabolites and Degradates

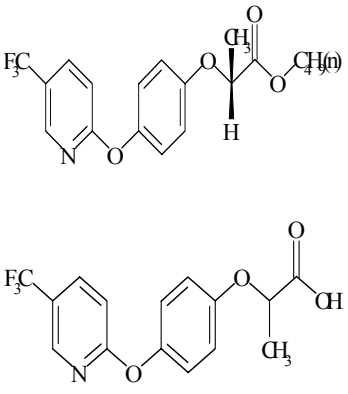
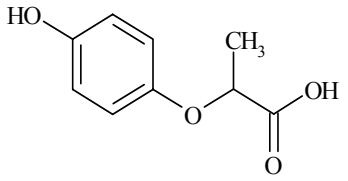
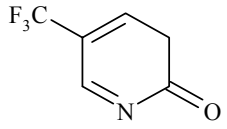
Chemical Name (other names in parenthesis)	Commodity	Percent TRR (PPM) [1]		Structure
		Phenyl Label	Pyridyl Label	
Fluazifop-P-butyl (free and conjugated) 2-(4-[5-(trifluoromethyl-2-pyridinyloxy] phenoxy) propionic acid	Carrot Roots	63.1%	43.5%	
	Celery Stem	42.4%	39.6%	
	Soybean	28%	--	
	Ruminant	--	36.9% in muscle	
		--	31.8% in fat	
		--	61.0% in kidney	
		--	61.7% in liver	
		--	67.7 in milk	
	Poultry	51.3% in muscle	68% in muscle	
		69.7% in liver	65.9% in liver	
		91.5% in egg	55.8% in egg	
	Rat	26% in male feces	5.2% in female feces	
Compound III (free and conjugated) 2-(4-hydroxyphenoxy) propionic acid	Carrot Roots	10%	–	
	Celery Stems	4.2%	1.1%	
	Soybean	25.5%	--	
	Rat	<0.04% in male urine	<0.09% in female urine	

Table 3.4 Tabular Summary of Fluazifop-P-butyl Metabolites and Degradates				
Chemical Name (other names in parenthesis)	Commodity	Percent TRR (PPM) [1]		Structure
		Phenyl Label	Pyridyl Label	
Compound X 5-trifluoromethyl-2-pyridone	Carrot roots	--	1.0%	
	Celery Stems	--	2.8%	
	Soybean	–	--	
	Rat	not identified	not identified	
Carrot, MRID No. 00152494; 0.451-0.475 lb ai/A; ~0.6x rate; or 0.219 lb ai/A; 0.3x rate; mature carrot roots (carrot tops were not collected for analysis); 46 days. Celery, MRID No. 40693102; phenyl label 0.56 lb ai/A; 0.75x rate; pyridyl label 0.70 lb ai/A; 0.9x rate; mature celery plants; 30 days. Soybean, MRID Nos. 41994701-41994703; 0.91 lb ai/A; 1.8x rate; mature soybean (foliage was not collected or analyzed). Ruminant (cattle), MRID No. 00093842; 2.49 ppm; 0.55x MTDB; 7 days. Poultry (hens), MRID No. 00093844; phenyl label 2.6 ppm; 2.6x MTDB; pyridyl label 2.2 ppm; 2.2x MTDB; 14 days. Rat, MRID No. 00093824; 1 mg/kg in a single dose; 48 hours.				

3.5 Toxicity Profile of Major Metabolites and Degradates

Based on their structures, the Metabolism Assessment Review Committee (MARC) was unable to conclude that the major metabolites of fluazifop-P-butyl will be significantly less toxic than the parent and therefore, recommended that for risk assessment purposes, the residues of concern are parent, fluazifop acid (free and conjugated), 5-trifluoromethyl-2-pyridone, and 2-(4-hydroxyphenoxy) propionic acid (free and conjugated). There are no specific toxicity concerns for all other minor metabolites. See *Fluazifop-P-butyl. Report of the Metabolism Assessment Review Committee. PC Code: 122809. DP Barcode: 298939. Sherrie L. Kinard, David Anderson, and William P. Eckel. July 8, 2004.*

3.6 Summary of Residues for Tolerance Expression and Risk Assessment

The tolerance expression includes the parent and fluazifop acid (free and conjugated). Several other major metabolites (> 10% total radioactive residue) have been identified in radio-labeled plant and animal metabolism studies and are included in the risk assessment. These metabolites are considered to be of equivalent toxicity to the parent.

No Codex maximum residue levels (MRLs) have been established for residues of fluazifop-P-butyl or fluazifop-butyl; therefore, issues of compatibility do not exist.

The following Canadian MRLs have been established for residues of fluazifop-butyl, calculated as the acid:

soybeans, strawberries . . . . . 1 ppm

mustard . . . . . 0.3 ppm
flax, solin . . . . . 0.2 ppm
eggs, meat, meat by-products and fat of cattle, goats, hogs, horses, poultry and sheep . 0.05 ppm
milk . . . . . 0.01 ppm

No Mexican MRLs have been established for residues of fluazifop-P-butyl.

3.6.1 Tabular Summary

Table 3.6.1 Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	Parent, Fluazifop acid (free and conjugated), 5-trifluoromethyl-2-pyridone, and 2-(4-hydroxyphenoxy) propionic acid (free and conjugated)	Parent and Fluazifop acid (free and conjugated)
	Rotational Crop	Inadequate data/No decision	Inadequate data/No decision
Livestock	Ruminant	Parent and Fluazifop acid (free and conjugated)	Parent and Fluazifop acid (free and conjugated)
	Poultry	Parent and Fluazifop acid (free and conjugated)	Parent and Fluazifop acid (free and conjugated)
Drinking Water		Parent and Fluazifop acid	Not Applicable

3.6.2 Rationale for Inclusion of Metabolites and Degradates

Based on their structures, MARC was unable to conclude that the major metabolites in plants will be significantly less toxic than the parent and therefore, recommended that for risk assessment, the residues of concern are parent, fluazifop acid (free and conjugated), 5-trifluoromethyl-2-pyridone, and 2-(4-hydroxyphenoxy) propionic acid (free and conjugated). There are no specific toxicity concerns for all other minor metabolites. The analytical method detects parent and fluazifop acid (free and conjugated). MARC concluded that for tolerance expression, parent and fluazifop acid (free and conjugated) are the residues of concern since they are adequate to determine misuse.

MARC concluded that 2-(4-hydroxyphenoxy)-5-trifluoromethyl pyridine can be excluded for livestock based on the following: 1) the absolute residue value is relatively low (about 0.01 ppm); 2) it is not likely to be significantly more toxic than the parent; 3) kidney and liver are not high consumption items. In the poultry study (both phenyl and pyridyl-^{14}C label), fluazifop-acid was identified as the only major component in all matrices. Therefore, the residues of concern for risk assessment and tolerance expression in livestock are parent and fluazifop acid (free and conjugated).

A ratio adjustment to account for additional metabolites of concern was calculated from

the carrot, celery, and soybean metabolism studies that were presented to MARC. The MARC suggested using the total radioactive residue ratio of the additional metabolites of concern to the parent in order to assess the potential dietary risks associated with fluazifop-P-butyl use. In doing so, the dietary assessments are considered to be conservative since they assumed tolerance level residues with the ratio adjustment (calculated from TRRs) accounting for the additional metabolites of concern and 100%CT (acute only) for most commodities, and default processing factors. These assessments do not need to be further refined at this time; however, they could be further refined by using field trial or monitoring data and/or processing/or preparation/cooking data to refine the default processing factors.

Adequate metabolism data are not available at this time. In the unacceptable celery metabolism study, leaves had the higher residues; however, in carrots and soybean, only roots and soybean portions were analyzed. Therefore, HED does not know the distribution of residues.

Plants:. Both pyridyl label and phenyl label metabolism studies were conducted on plants. Fluazifop acid (free and conjugated), 5-trifluoromethyl-2-pyridone, and 2-(4-hydroxyphenoxy) propionic acid are the major residues (>10% TRR). Based on their structures, MARC was unable to conclude that these major metabolites will be significantly less toxic than the parent and therefore, recommended that for risk assessment, the residues of concern are parent, fluazifop acid (free and conjugated), 5-trifluoromethyl-2-pyridone, and 2-(4-hydroxyphenoxy) propionic acid (free and conjugated). There are no specific toxicity concerns for all other minor metabolites. The analytical method detects parent and fluazifop acid (free and conjugated). MARC concluded that for tolerance expression, parent and fluazifop acid (free and conjugated) are the residues of concern since they are adequate to determine misuse.

Livestock: Livestock metabolism study conducted on dairy cattle dosed with a mixture of [phenyl-U-^{14}C]fluazifop-butyl and [pyridyl-^{14}C]fluazifop-butyl at 2.49 ppm in the diet (0.55x MTDB) indicated that fluazifop (free and conjugated) was identified as the major component in all cow tissues, at 36.9% TRR (<0.001 ppm) in muscle, 31.8% TRR (<0.002 ppm) in fat, 61.0% TRR (0.024 ppm) in kidney, and 61.7% TRR (0.014 ppm) in liver. The majority of the radioactivity in milk was lipophilic in nature and was converted to fluazifop upon base hydrolysis (67.7% TRR, 0.030 ppm); TLC analysis of the major extract prior to base hydrolysis indicated that the major residue in milk was a triglyceride ester(s) of fluazifop. The metabolite 2-(4-hydroxyphenoxy)-5-trifluoromethyl pyridine was the only other metabolite identified, at 11.8% TRR (0.005 ppm) in kidney and 10.3% TRR (0.002 ppm) in liver. MARC concluded that 2-(4-hydroxyphenoxy)-5-trifluoromethyl pyridine can be excluded based on the following: 1) the absolute residue value is relatively low (about 0.01 ppm); 2) it is not likely to be significantly more toxic than the parent; 3) kidney and liver are not high consumption items. In the poultry study (both phenyl and pyridyl-^{14}C label), fluazifop acid was identified as the only major component in all matrices. Therefore, the residues of concern for risk assessment and tolerance expression in livestock are parent and fluazifop acid (free and conjugated).

Rotational Crop: No decision was made on rotational crops due to no information being available on identification of metabolites. Radioactive residues (expressed as fluazifop-butyl equivalents) were <0.01 ppm in all crops grown to maturity in ^{14}C-Phenyl labeled fluazifop-butyl treated soil at (0.33 x Rate) and hence no rotational crop tolerances may be needed. However,

wheat straw and sugar beet foliage had 0.10 ppm and 0.03 ppm total residues, respectively, following treatment with pyridyl labeled fluazifop-butyl with the same rate.

Drinking Water: Environmental fate studies indicated that parent is not mobile and not persistent. Aerobic soil metabolism studies showed that the half-life of the parent ester is on the order of a few hours. The major degradates (>10% of applied radiation in any fate study) are fluazifop-acid and 5-trifluoromethyl-2-pyridone. Fluazifop acid is not very persistent in aerobic soil (half-lives 11 to 26 days) but is stable in flooded (anaerobic) soil, and in hydrolysis studies. Fluazifop-acid is considered to be mobile (K_{oc} 8.3 to 51) and therefore can potentially reach surface and ground water. MARC recommended to include fluazifop-acid in the drinking water assessment. MARC concluded that 5-trifluoromethyl-2-pyridone can be excluded based on the following: 1) the exposure level is very low relative to fluazifop acid based on its later formation in the degradation process; 2) there is not obvious evidence of it being highly toxic in the rat based on the results of the parent toxicology studies and its presence as a rat metabolite (albeit at a very low level); 3) no special concerns were identified in literature; and 4) it is sufficiently protective to regulate the parent and the fluazifop acid. MARC concluded that the residues of concern for drinking water assessment are parent and fluazifop acid.

4.0 Hazard Characterization/Assessment

4.1 Hazard and Dose Response Characterization

4.1.1 Database Summary

4.1.1.1 Critical Studies (animal, human and general literature)

Acute -	Oral, Dermal, Inhalation, Eye and skin irritation, Dermal sensitization with fluazifop-butyl and fluazifop-P-butyl
Subchronic -	Oral rat with fluazifop-butyl and fluazifop-P-butyl, Oral dog with fluazifop-butyl, Dermal 21-day rabbit with fluazifop-butyl, Inhalation - no studies available.
Chronic-	Chronic/Cancer rat with fluazifop-butyl, Cancer hamster with fluazifop-P-butyl, Oral dog with fluazifop-butyl
Developmental-	Two in the Sprague Dawley rat with fluazifop-butyl and three in the Wistar rat with fluazifop-P-butyl. One in the NZW Rabbit with fluazifop-butyl and one in the NZW rabbit with fluazifop-P-butyl.
Reproduction-	Two-generation in rats with fluazifop-butyl
Metabolism-	Rat, dog, human with fluazifop-butyl and comparative in the rat with fluazifop-butyl and fluazifop-P-butyl, and hamsters with fluazifop-P-butyl.

Dermal penetration- Human study

Literature Studies- Literature studies regarding information for which similar, but more detailed, reports were submitted to the Agency.

4.1.1.2 Mode of action, metabolism, toxicokinetic data

Fluazifop-butyl is a herbicide with mixed isomeric [RS] content, while fluazifop-P-butyl is the purified [R] enantiomer, the only herbicide supported for reregistration. Metabolism studies have been conducted in the rat with fluazifop-butyl, and absorption, excretion and confirmatory metabolism studies in the dog and human with fluazifop-butyl, and hamster with fluazifop-P-butyl. Comparative metabolism studies in the rat show that both products are rapidly hydrolyzed to fluazifop acid and the [S] enantiomer is rapidly converted to the [R] enantiomer in the blood, yielding similar toxicities within animal variation. Peroxasome proliferation was shown in rat and mouse, and to a lesser extent in the hamster *in vivo* and human liver cells *in vitro*. The dermal absorption factor in humans is 9% for low exposures and 2% for high exposures.

4.1.1.3 Sufficiency of studies/data

The toxicity data base on fluazifop-butyl is essentially complete with sufficient toxicity data on fluazifop-P-butyl to show equivalence in animal toxicity. The toxicity data base is adequate for FQPA assessment, endpoint selection and dose-response evaluation of both products. Though the assessment team initially required a confirmatory 28-day inhalation study (a routine requirement when there is potential inhalation exposure), this requirement is waived. Fluazifop-P-butyl has low volatility, is not an eye or skin irritant in acute or 21-day dermal studies, and is not a skin sensitizer. Fluazifop-P-butyl is likely to show similar toxicity by the inhalation route and the oral route, because it is metabolized by blood to the acid form and excreted as the acid form. The use pattern and exposure pattern for the residential handler show high MOEs, well above the level of concern using endpoints based on oral exposure. The data are relatively consistent among the rat with fluazifop-butyl and fluazifop-P-butyl, dog with fluazifop-butyl, hamster with fluazifop-P-butyl and human studies with fluazifop-butyl, with some variation probably within animal variation, although all endpoints were not evaluated with all species with both products.

4.1.2 Toxicological Effects

Fluazifop-butyl and fluazifop-P-butyl have low acute toxicity in two species by the oral, dermal and inhalation routes and are not dermal sensitizers.

Chronic and subchronic studies with fluazifop-butyl or fluazifop-P-butyl show that the rat is more sensitive to toxic effects than the dog, rabbit or hamster, possibly due to longer retention time of the main metabolite (fluazifop acid) in the rat due to biliary excretion and reabsorption. The kidney and liver are the target organs and the toxicity is expressed as exacerbation of the age related kidney toxicity and liver toxicity in the presence of peroxasome proliferation. However, the extensive and age related nephropathy in control groups complicate this conclusion with regard to the kidney. At the highest dose in the chronic studies,

hematological effects, gastrointestinal lesions, and cataracts were noted in the dog. Less definitive effects were noted with vacuolation of the adrenal glands. Cholesterol depression was noted at the two top doses in the male dog and rat and to a lesser degree in the female. An unusual finding was noted in the older toxicity studies with fluazifop-butyl in the rabbit, rat, and dog. Frequently death was seen in some animals at the highest dose levels, but few histological effects being noted on surviving animals. These chronic studies showed an exacerbation of age related nephropathy, which may be related to the deaths. In general, longer duration studies show effects at lower dose levels.

The two-generation reproduction study in the rat showed less ambiguous effects than the chronic studies. The testes and uterus or ovaries were target organs in the reproduction study and hamster study, with kidney and liver effects at higher doses. The testes and epididymal weight and uterine and pituitary weight decrement were selected for the chronic endpoint for risk assessment due to the problems in the interpretation of the older age related nephropathy in chronic and subchronic studies. In addition, the NOAEL from the study on reproduction was essentially the same as the NOAEL from the chronic study.

The treatment related malformations (diaphragmatic hernia) found in an earlier study were confirmed at the highest dose tested in a 160 litter per group study in the Sprague Dawley rat, which also showed dose-related fetal weight decrement and delayed ossification at the LOAEL. The maternal toxic LOAEL was selected from among 3 developmental toxicity studies in the Wistar rat, which showed definitive maternal toxicity at the highest dose tested in one study.

There were no carcinogenicity concerns in acceptable studies in the rat with fluazifop-butyl and in the hamster with fluazifop-P-butyl. The hamster was selected for cancer study because peroxasome proliferation in the hamster liver more closely resembled that found for human liver cells. There were no mutagenicity concerns with fluazifop-butyl or fluazifop-P-butyl.

4.1.3 Dose-response

A statistically significant, but marginally adequate dose-response was shown in the testes weight, and epididymal weight, decrement in the parental and F1 generation in the adult rat, potentially due to reduced sperm content. The cancer study in hamsters showed a good dose-response in testes weight decrement. Since the statistically significant effects were seen in the male P0 and F1 parents and in the hamster study, the effects were considered treatment related. The testicular endpoint from the reproduction study was selected for the chronic RfD, intermediate-term oral incidental exposure, intermediate and long-term dermal and inhalation exposure. Other studies showed testes weight decrement and epididymal effects at higher dose levels, but there were only equivocal histological effects shown. Although extensive short-term studies on the testes weight decrement and epididymal effects were conducted, all failed to show that the effect was incidental or find an explanation for the effect. However, the more sensitive studies on sperm count were not among the extra studies conducted. An acceptable negative study of sufficient duration on sperm parameters would add confidence to the possibility that the testes and epididymal weight decrement seen in the rat reproduction study were incidental and not reproducible. The uterine weight decrement seen in the reproduction study showed a good

dose-response and was supported by a dose-response in the pituitary weight decrement at the same doses. In addition, in the hamster, hyperplasia in the ovary was seen at high dose levels. One of the subchronic studies in the rat with fluazifop-P-butyl showed testicular weight decrement, while the other one with fluazifop-butyl did not at approximately the same doses as in the reproduction study; at the highest dose tested in the subchronic study with fluazifop-butyl absolute testes weights were increased 30%. The reason is unknown, but may be due to animal variation or other unknown factors such as edema.

The testes and epididymal weight decrement and uterine and ovarian effects suggest possible endocrine related effects. However, negative *in vitro* studies suggest estrogen and androgen hormones were not involved. Agonistic and antagonistic studies with fluazifop-butyl, fluazifop-P-butyl and the fluazifop acid metabolite were conducted in yeast cells containing human estrogen and androgen receptors. No receptor activity was found with any of the test materials over a sufficiently wide concentration range.

The acute RfD and short-term incidental oral, and short-term dermal and inhalation exposure endpoints were selected from the developmental data base which includes 7 developmental toxicity studies: 2 with fluazifop-butyl in Sprague-Dawley rats; 3 with fluazifop-P-butyl in Wistar rats; 1 with fluazifop-butyl in New Zealand rabbits; and 1 with fluazifop-P-butyl in New Zealand rabbits. There was evidence (quantitative) of increased susceptibility in the fetuses of two strains of rats exposed *in utero* to fluazifop-butyl. Developmental toxicity characterized as delays in skeletal ossifications were seen in the absence of maternal toxicity relatively consistently in all five rat studies. However, the concern is low for the increased susceptibility seen in the rats based on the following considerations: the endpoint of concern (delayed ossifications) is a developmental delay and not a malformation or a variation which are considered to be more serious in nature. The delayed ossification in a given parameter showed considerable variation in the incidence among the five studies requiring a weight of evidence to determine the appropriate NOAEL/LOAEL among the five rat studies. There was no evidence (quantitative or qualitative) of increased susceptibility following *in utero* exposures to rabbits.

The dose-related kidney and liver toxicity shown in the older subchronic and chronic studies was expressed as exacerbation of age related kidney toxicity and liver toxicity. Tests show that this toxicity was in the presence of peroxasome proliferation. However, the extensive and age related nephropathy in control groups complicate this conclusion with regard to the kidney. A possible treatment related slight increase in chronic nephropathy was noted only at the highest dose tested in the more recent study of reproduction in the rat.

The uncertainty factors used with all endpoints were 10X for inter-species extrapolation and 10X for intraspecies variation for a total of 100X.

4.1.4 FQPA

The FQPA factor was reduced to 1X. No increased offspring sensitivity over parent was seen the rabbit pre-natal developmental studies or the post-natal reproduction study. Although malformed fetuses were seen at high dose levels in the absence of maternal toxicity in the rat developmental toxicity studies, the definitive developmental endpoint in five developmental studies was selected based delayed ossification and fetal weight decrement at much lower doses

(100 fold lower). No evidence of neurotoxicity was seen and no acute, subchronic neurotoxicity, or developmental neurotoxicity (DNT) studies were recommended.

Table 4.1a:Acute Toxicity Data on FLUAZIFOP-BUTYL & FLUAZIFOP-P-BUTYL.

Guideline No./ Study Type	MRID No.	Results	Toxicity Category
Acute Studies with Fluazifop-butyl (PC 122805)			
870.1100 Acute oral toxicity/rats (PP009; 97.2%)	00162439 (1983)	LD50 = 1940 mg/kg (males) ± 1193-2758 mg/kg LD50 = 2653 mg/kg (females) ± 1764-3625 mg/kg	III
870.1200 Acute dermal toxicity/rabbits (PP009; 97.2%)	00162439 (1983)	LD50 > 2mL/kg (males and females) or approximately 2000 mg/kg	III
870.1300 Acute inhalation toxicity/rats (PP009; 97%) 79/ISK034/387	46082901, same as 41563701 (1979)	LC50 > 2.3 mg/L for 43% with a particle size <5 µm LC50 >4.37 mg/L for 83% with a particle size <10 µm	III
870.2400 Acute eye irritation/rabbit (PP009; 93.3%) 79/ILK9/068	00088855 (1979)	Non-irritating	IV
870.2500 Acute dermal irritation/rabbit (PP009; 93.3%) 79ILK8/056	00088853 (1979)	Mild erythema at 72 hours	IV
870.2600 Skin sensitization/GP (PP009; 99.6%) 80/ILK026/349	00088854 (1980)	Not a dermal sensitizer	
Acute Studies with Fluazifop-P-butyl (PC 122809)			
Guideline No./ Study Type	**MRID No.**	**Results**	**Toxicity Category**
870.1100 Acute oral toxicity/rats (PP005; 93.7% & 86.3%)	00162440 (1984)	LD50 = 3680 mg/kg for males rats LD50 = 2451 mg/kg for female rats	III III
870.1200 Acute dermal toxicity/rabbits (PP005; 93.7% & 86.3%)	00162440 (1984)	LD50 > 2000 mg/kg or >1.73 mL/kg	III
870.1300 Acute inhalation [a] toxicity/rats (PP005; 24.6%) CTL/P/3331	41917904 (1991)	LC50 > 1.7 mg/L	III
870.2400 Acute eye irritation/rabbit (PP005; 86.3%) CTL/P/856	00162441 (1983)	Mild irritation, cleared within 3 days	IV
870.2500 Acute dermal irritation/rabbit (PP005; 86.3%) CTL/P/856	00162441 (1983)	Slight irritation, cleared within 72 hours	IV

Table 4.1a:Acute Toxicity Data on FLUAZIFOP-BUTYL & FLUAZIFOP-P-BUTYL.			
870.2600 Skin sensitization/GP (PP005; 99.6%) 80/ILK026/349	00162441 (1983)	Not a skin sensitizer	

[a] This study was conducted with a mixture of 24.6% fluazifop-P-butyl and 7.0% fenoxyprop-P-ethyl, however, the concentration fluazifop-P-butyl in the inhalation chamber was determined to be 1.7 mg/L. PPOO9 was used to indicate the technical grade of fluazifop-butyl. PPOO5 was used to indicate the technical grade of fluazifop-P-butyl.

Table 4.1b Subchronic, Chronic, Developmental, Reproductive and Other Toxicity Profile on Fluazifop-butyl [FB] and Fluazifop-P-butyl [FPB].

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 90-Day oral toxicity (rat) with FB	00093820 (1980) Acceptable/guideline 0, 10, 100, 2000 ppm M: 0, 0.7, 7.1, 144.5 mg/kg/day F; 0, 0.8, 8.0, 161.9 mg/kg/day	NOAEL=0.7 mg/kg/day LOAEL=7.1 mg/kg/day based on liver and kidney histopathology.
870.3100 90-Day oral toxicity (rat) with FPB	46158402 (1985) Acceptable/guideline 0, 10, 100, 2000 ppm —F: 0, 0.5, 5, 100 mg/kg/day	NOAEL=0.5 mg/kg/day LOAEL=5 mg/kg/day based on decreased spleen weight and decreased hematological parameters in males. Dose related testicular weight decrement and cholesterol depression were also seen.
870.3150 90-Day oral toxicity (dog) with FB	00093821 (1980) Acceptable/guideline 0, 5, 25, 125/250 mg/kg/day	NOAEL = 25 mg/kg/day LOAEL = 125/250 mg/kg/day based on multiple pathologies in 3 dogs (2 males and 1 female) killed at 1 month dosed at 250 mg/kg/day. Also seen were body weight loss gut lesions, severe eye lesions and hepatotoxicity. In remaining surviving dogs dosed at 125 mg/kg/day , mild to equivocal liver lesions were seen.
870.3150 90-Day oral toxicity (hamster) with FPB	46082902 (2001) Acceptable/guideline Males: 0, 19.5, 78.3 or 291.9 mg/kg/day Females: 0, 19.9, 79.0 or 319.6 mg/kg/day	NOAEL = M/F: 78.3/79.0 mg/kg/day LOAEL = M/F: 291.9/319.6 mg/kg/day based on decreased body weight/body weight gain and food efficiency in males and evidence of liver toxicity; centrilobular eosinophilia/loss of glycogen in males and females.
870.3200 21/28-Day dermal toxicity (rabbit) with FB	00093819 (1980) Acceptable/guideline 0, 100, 500, 2000 mg/kg/day	NOAEL = 100 mg/kg/day LOAEL = 500 mg/kg/day based on death in 1 male and at 2000 mg/kg/day, death 4 males and 5 females, possibly due to kidney failure.
870.3250 90-Day dermal toxicity (species)	Not required	

Table 4.1b Subchronic, Chronic, Developmental, Reproductive and Other Toxicity Profile on Fluazifop-butyl [FB] and Fluazifop-P-butyl [FPB].		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3465 90-Day inhalation toxicity (species)	Not required.	
870.3700a Prenatal developmental in (Sprague Dawley rats) with FB	0008857, 92067047 (1981) Acceptable/guideline 0, 10, 50, 200 mg/kg/day	**Maternal** NOAEL = 200 mg/kg/day LOAEL = None based on maternal weight decrement due to gravid uterine weight decrement. **Developmental** NOAEL=none LOAEL=10 mg/kg/day based on delayed ossification. **Malformations** NOAEL = 50 mg/kg/day LOAEL = 200 mg/kg/day based on diaphragmatic hernia.
870.3700a Developmental toxicity (Sprague Dawley rat) with FB	00088858, 92067048, 92967020 (1981) Acceptable/guideline 0, 1.0, 5.0, 10, 200 mg/kg/day with FB	**Maternal** NOAEL=200 mg/kg/day. LOAEL=None based on maternal weight decrement partially explained by gravid urine weight decrement. **Developmental** NOAEL=1 mg/kg/day. LOAEL=5 mg/kg/day based on fetal weight decrement and increased incidence of small fetuses and delayed ossification. **Malformations** NOAEL= 10 mg/kg/day LOAEL=200 mg/kg/day based on increased incidence of diaphragmatic hernia.
870.3700a Developmental toxicity (Wistar rats) with FPB	46158401 (1991) Acceptable/guideline 0, 0.5, 1.0, 20, 300 mg/kg/day	**Maternal** NOAEL=20 mg/kg/day LOAEL=300 mg/kg/day based on body weight gain decrement. **Developmental** NOAEL=1.0 mg/kg/day LOAEL=20 mg/kg/day based on delayed ossification in skull bones, cervical arches and centrum in fetuses and litters and delayed ossification in the manus and pes.
870.3700a Developmental Toxicity (Wistar rats) with FPB	46082903 (1989) Acceptable/guideline 0, 2, 5 or 100 mg/kg/day	**Maternal** NOAEL=100 mg/kg/day LOAEL= None based no maternal toxicity. **Developmental** NOAEL=2.0 mg/kg/day LOAEL=5.0 mg/kg/day based on based on dose related delayed ossification in skull bones [occipital and parietal] in fetuses and litters.
870.3700a Developmental Toxicity (Wistar rats) with FPB	46082013 (1990) Acceptable/guideline 0, 2.0, 5.0, 100 mg/kg/day	**Maternal** NOAEL=100 mg/kg/day LOAEL= None based on no toxic effects **Developmental** NOAEL=2.0 mg/kg/day LOAEL=5.0 mg/kg/day based on delayed ossification in skull bones, sternebrae bipartite, sternebrae and calcenum unossified in fetuses and litters.
The overall conclusions based on a weight of evidence on the five studies of developmental toxicity in the rat were a NOAEL/LOAEL = 2.0/5.0 mg/kg/day based on fetal weight decrement and delayed ossification.		

Table 4.1b Subchronic, Chronic, Developmental, Reproductive and Other Toxicity Profile on Fluazifop-butyl [FB] and Fluazifop-P-butyl [FPB].

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3700b Developmental toxicity (NZW rabbit) with FB	00088856, 92067049, 92067021 (1981) Acceptable/guideline 0, 10, 30, 90 mg/kg/day	**Maternal** NOAEL=30 mg/kg/day LOAEL=90 mg/kg/day based on abortions. **Developmental** NOAEL=30 mg/kg/day LOAEL=90 mg/kg/day based on nominal increases in delayed ossification, total litter loss, abortions, small fetuses, cloudy eyes all above mean or range of historical controls
870.3700b Developmental toxicity (NZW rabbits) with FPB	46082904 (1993) Acceptable/guideline 0, 2, 10, 50 mg/kg/day	**Maternal** NOAEL=10 mg/kg/day LOAEL=50 mg/kg/day based death, abortions and body weight loss **Developmental** NOAEL=10 mg/kg/day LOAEL=50 mg/kg/day based on increased incidence of 13th rib and delayed ossification in sternebrae 2.
870.3800 Reproduction and fertility effects (rats) with FB	00088859, 92067050 (1981) Acceptable/guideline 0, 10, 80, 250 ppm M/F: 0/0, 0.74/0.88, 5.8/7.1, 21.7/17.5 mg/kg/day	**Parental/Systemic** NOAEL = M/F 0.74/7.1 mg/kg/day LOAEL = M/F 5.8/ 21.7 mg/kg/day based on decreased spleen wt. in males & increased absolute & relative liver & kidney wts. & geriatric nephropathy in females. **Offspring** NOAEL = 7.1 mg/kg/day LOAEL = 21.7 mg/kg/day based on pup viability in f1 and f2 pups during lactational day 1, 4, 11, 18 & 25 and decreased f2 pup weight on lactational day 25. **Reproductive** NOAEL = M/F 0.74/0.88mg/kg/day LOAEL = M/F 5.8/7.1 mg/kg/day based on decreased abs. & rel testes & epididymal weight and in females decreased pituitary & uterine weights. Sperm counts not available.
Conclusions on the 2-generation study on reproduction in the Sprague Dawley rat: The cause of the dose related testes wt decrease in the P0 and F1 generations has not been demonstrated, but no sperm counts, morphology, motility have been conducted to date. Extensive short term studies on testes weight, testes histopathology, and endocrine effects (MRID# 46082911, 46082916, 46082917,46082920 & 46082920, see table 4.1d) failed to find the reason for the testes weight decrement in the rat and hamster. However, since the most sensitive tests for effects on sperm were not conducted (sperm count, motility and morphology as indicated in the 1996 guidelines), it is concluded that testes weight decrement from possible decrements in sperm seen in the rat reproduction and the chronic study in hamsters have not been adequately eliminated. The histology on the testes does not support an effect, but histology is insufficiently sensitive to detect an slight effect.		
870.4100a Chronic toxicity (rats)	870.4300 satisfies the requirement	
870.4100b Chronic toxicity (dog) with FB	00131462, 00131463, 92067018 (1982) Acceptable/guideline 0, 5, 25, 125 mg/kg/day	NOAEL = 5 mg/kg/day LOAEL = 25 mg/kg/day based on marginally increased incidence adrenal fatty vacuolation & increased incidence of thymic involution and at 125 mg/kg/day death of 4/6 males and 2/6 females, eye, gastrointestinal tract lesions, adrenal and bone marrow pathology & thymic involution.

Table 4.1b Subchronic, Chronic, Developmental, Reproductive and Other Toxicity Profile on Fluazifop-butyl [FB] and Fluazifop-P-butyl [FPB].		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.4200 Carcinogenicity (hamster) with FPB	4534501, 46082905 (2001) Acceptable/guideline 0, 0, 200, 750, 3000 ppm M: 0, 0, 12.5, 47.4, 193.6 mg/kg/day F: 0, 0, 12.1, 45.5, 181.4 mg/kg/day	NOAEL =M/F 12.5/12.1 mg/kg/day LOAEL = 47.5/45.5 mg/kg/day based on based on increased incidence of males with reduced sperm, testicular degeneration, eye cataract changes, liver inflamation and gall stones and in females, increased incidence of ovarian stroma cell/sex chord hyperplasia. **No evidence of carcinogenicity**
870.4300 Chronic/Carcinogenicity (rat) with FB	41563703 (1985) Acceptable/guideline 0, 2, 10, 80, 250 ppm M: 0, 0.10, 0.51, 4.15, 12.3 mg/kg/day F: 0, 0.13, 0.65, 5.2, 16.0 mg/kg/day	NOAEL =M/F 0.51/5.2 mg/kg/day LOAEL =M/F 4.15/16.0 mg/kg/day based on increased mortality & nephropathy exacerbated by respiratory stress, and in females possible increased basal and/or follicular/luteal cysts. **No evidence of carcinogenicity**
870.6100a Acute neurotoxicity in hens with FB	00093818 (1981) Acceptable/guideline 0, 3750, 7500 or 15000 or 15000 mg/kg	Fluazifop-butyl exposed hens showed no evidence of delayed neurotoxicity.
870.6200a Acute neurotoxicity screening battery	Not required	
870.6200b Subchronic neurotoxicity screening battery	Not required	
870.6300 Developmental neurotoxicity	Not required	
870.7485 Metabolism and pharmacokinetics (rats) with FB	00093822 through 00093828 (1981) Acceptable/guideline 1 mg/kg and 1000 mg/kg	Fluazifop-butyl is rapidly hydrolyzed to fluazifop acid by blood enzymes and excreted as the acid and its conjugates in the urine of males and females. Due to biliary excretion parent compound, fluazifop acid and its conjugates are excreted in the feces of males at much higher proportions than in feces of the female. Excretion was complete in 7 days, with the exception of small amounts in the fat in some rats.
870.7600 Dermal penetration (human)		MRID# 46082918 a human study/NG satisfies guideline 870.7600.

Table 4.1b Subchronic, Chronic, Developmental, Reproductive and Other Toxicity Profile on Fluazifop-butyl [FB] and Fluazifop-P-butyl [FPB].

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
NG Comparative metabolism with FB and FPB in rats	00162445, 0012446 (1983) Acceptable/NG 1 mg/kg	FB is hydrolyzed and the [S] enantiomer is converted to the [R] enantiomer. Whether fluazifop-butyl [RS] (50:50) or fluazifop-P-butyl [S] (90:10) is administered, within a hour the blood contained a mixture composed of fluazifop acid in a ratio of [R] 95% and [S] 3%. The two products behaved similarly and reached the same equilibrium within experimental error.
NG Plasma level time course with FB and FPB in rats	46082910 (1998) Acceptable/NG 200 mg/kg	The time course of plasma levels and elimination of the acid metabolite were similar for both fluazifop-butyl and fluazifop-P-butyl. Plasma levels of the acid from both isomers were much higher in males than in females. The data support previous studies.
NG Absorption and excretion study in hamsters with FPB	46082923 (2002) Acceptable/NG 0, 200, 750, 3000 ppm	The study was conducted in two phases, Phase 1- single dose followed by 3 days of unlabeled test material and Phase 2 - 24 hour feeding of labeled test material followed by 3 day of unlabeled test material. Data were consistent with excretion data from other species. The system appeared saturated, since the ratio of the 3000/200 ppm dose levels was much lower than the ratio of respective plasma levels, especially for males.
NG Absorption, excretion and tissue retention in mice with FB	46082925 (1992) Acceptable/NG 1 and 150 mg/kg	Male mice excreted proportionally more in feces and less in urine than females. Although males excreted more than females in the feces and females excreted more than males in the urine, the difference between males and female mice was smaller than with male and female rats. The study showed individual variability in excretion, similar to that found in the rats, dog and human, although analytical deviation may have explained part of the variation.
NG Absorption and excretion in dogs with FB	0093829 (1981) Acceptable/NG 1 mg/kg	One dog showed delayed absorption. Excretion rate similar to females rats. No evidence of biliary excretion.
NG Peroxasome proliferation in mice, rats, hamsters and humans with FPB	46082919 (1988) Acceptable/NG 0, 80, 250, 1000 or 2000 ppm	*In vivo* and *in vitro* peroxasome proliferation was studied in the mouse, rat and hamster and in vitro human hepatocytes. Proliferation in hepatocytes from the greatest to the smallest was: mice > rats > hamster >> human. No increase in cell replication was seen at any dose.

Table 4.1b Subchronic, Chronic, Developmental, Reproductive and Other Toxicity Profile on Fluazifop-butyl [FB] and Fluazifop-P-butyl [FPB].		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
NG Androgen/estrogen activity with FPB & acid; FB & acid metabolite	46082916 (2001) Acceptable/NG	No agonist or antagonist activity was detected for FPB or FB or their acid metabolites. Using recombinant yeast strains expressing human androgen receptor or estrogen receptor, the intrinsic androgenic, anti-androgenic, estrogenic, anti-estrogenic activity of FPB, FB and their respective acid metabolites have been assessed by absorbance in a transcription assay. Positive antagonists were hydrotamoxifen and flutamide, which induced appropriate antagonic activity. Agonistic activity assessed by comparison to 17β-estradiol and dihydrotestosterone; antagonic activity was assessed by inhibition of 17βestradiol and dihydrotestosterone activity. No agonist or antagonic activity was found within 7 orders of magnitude (oom) greater than the conc. of estradiol transcription, 4 oom greater for inhibition of estradiol transcription and 6 oom for agonistic activity of dihydrotestosterone and up to 156 µM antagonist activity by a dose related decrease in dihydrotestosterone-mediated androgenic activity.
NG Dermal absorption in humans with FB	46082918, 46082927, 4153704 (1991) Acceptable/NG 2 mg & 200 mg/person	Dermal absorption was 8.6% at 2 mg/person and 1.9% at 200 mg/person
NG Dermal multidose in humans with FB	46082908 (1989) Acceptable/NG 20 mg	Six male humans were dermally dosed for 5 days at 20 mg/person and the pharmacokinetics followed The study was consistent with other studies in humans, dogs and female rats. Estimated one-half-life was 12.6 to 17.3 hours, which was much more uniform than seen in other studies. There was no evidence of accumulation of the dose.
NG Oral absorption, metabolism and excretion in men with FB	00131464 (1983) Acceptable/NG 0.07mg/kg	Metabolism was similar to the female rat and dog. Absorption was delayed in one man and excretion in the urine was variable with no evidence of biliary excretion.

Table 4.1c: Mutagenicity data summaries on Fluazifop-butyl (FB) and fluazifop-P-butyl (FPB)
Adequacy of data base for Mutagenicity: No mutagenic potential was seen in adequately conducted pre-1991 guideline mutagenicity studies (*in vivo and in vitro*) on fluazifop-P-butyl [FPB] or fluazifop-butyl [FB]. A structural analogue {haloxyfop-methyl [methyl 2-[4-[[3-chloro-5-(trifluromethyl)-2-pyridinyl] oxy]phenoxy]propinonate]} of fluazifop-P-butyl showed no mutagenic potential.
1. Gene Mutation

Table 4.1c: Mutagenicity data summaries on Fluazifop-butyl (FB) and fluazifop-P-butyl (FPB)	
Guideline 870.5100, Ames/*Salmonella typhimurium,* reverse mutation MRID 00162443 Acceptable Test material [FB]	In a reverse gene mutation assay in bacteria (MRID 00162443, 92067023), histidine deficient strains TA98, TA100, TA1535, TA1537, TA1538 of *S. typhimurium* were exposed to fluazifop-butyl (96.8% a.i., batch/lot# P25) in the presence and absence of mammalian metabolic activation by plate incorporation. Negative with and without S9 up to the limit dose of 5000 µg/plate.
Guideline 870.5100, Ames/*Salmonella typhimurium,* reverse mutation MRID 00162442 Acceptable Test material [FPB]	In a reverse gene mutation assay in bacteria (MRID 00162442, 92067013), histidine deficient strains TA98, TA100, TA1535, TA1537, TA1538 of *S. typhimurium* were exposed to fluazifop-butyl (93.6% a.i., batch/lot# P8) in the presence and absence of mammalian metabolic activation by plate incorporation. Negative with and without S9 up to the limit dose of 5000 µg/plate (insoluble at 5000µg/plate).
Guideline 870.5300, Mouse lymphoma cell test Acceptable Test material [FB]	In a mammalian cell gene mutation assay (MRID 00116678), heterozygous TK+/- P 388 mouse lymphoma cells cultured *in vitro* were exposed to fluazifop-butyl, (99.6% a.i., batch/lot # ADGM/1021/79) at concentrations of 0, 0.25, 2.5, 25, 250 or 2500 µg/mL in the presence and absence of mammalian metabolic activation, S9, for 30 minutes. Negative with and without S9 up to cytotoxic doses.
Guideline 870.5300, Mouse lymphoma L5178Y TK+ test Acceptable Test material [FPB]	In a mammalian cell gene mutation assay (MRID 46082906), mouse lymphoma L5178Y TK+ cells *in vitro* were exposed 4 hr to fluazifop-P-butyl at 0, 100, 200, 500, 700, 1000 or 1500 µg/mL with and without S9 activation. In second assay the cells were exposed to 0, 100, 200, 500, 700 or 1000 µg/mL with and without S9 activation. Test was negative with and without S9 activation up to and including excessive precipitation.
2. Cytogenetics	
Guideline 870.5375; *In vitro* chromosomal aberrations in human blood lymphocytes. (1985) Acceptable Test material: [FPB]	In independently performed mammalian cell cytogenetic assays (chromosome aberration) (MRID 41555202), lymphocyte cultures prepared from human peripheral blood were exposed to fluazifop-p-butyl (R-enantiomer, 93.8% a.i.; CTL reference # Y02746/001/008) in dimethyl sulfoxide for 4 hours at concentrations of 0, 1, 10, 100, 500, or 1000 µg/mL both in the presence and absence of S9-activation. Cells were harvested at 27 hours after initiation of treatment. The was no evidence of chromosome aberration induced over background in the presence or absence of S9-activation at toxic doses.
Guideline 870.5385, *In vivo* rat mammalian cytogenetics; bone marrow chromosomal aberrations (1980) Acceptable Test material: [FB]	In independent bone marrow chromosome aberration assays (MRID 00088861), 10 male CD rats/dose were treated via oral gavage (10 mL/kg) either once (acute) or daily for 5 consecutive days (sub-acute) with fluazifop-butyl (94.5% a.i.; Lot/Batch #: CTL Compound code: Y00083/001/006), in corn oil at doses of 0, 21.0, 67.2, or 210.0 mg/kg. Bone marrow cells were harvested at 6 or 24 hours after treatment in the acute study, and at 6 hours after treatment in the sub-acute study. There was no evidence of chromosome aberration induced over background at toxic doses.

Table 4.1c: Mutagenicity data summaries on Fluazifop-butyl (FB) and fluazifop-P-butyl (FPB)	
Guideline 870.5450, Mouse Dominant lethal test (1980) Unacceptable: Top dose not sufficiently toxic Test material: [FB]	In a dominant lethal assay (MRID 00088862) [PP009, fluazifop-butyl (97.0% a.i., batch/lot # 310M)] was administered to 25 CD-1 male mice/group by corn oil gavage (10 mL /kg) at dose levels of 0, 28.7, 91.8 or 287 mg/kg/day for 5 days for the first mating. Based on the results of the first mating, subsequent matings were based on 15 of the 25 dosed males. These 15 males were mated with 30 females in 8 sets and the females examined for dominant lethal effects (resorptions) at day 15 of pregnancy. The investigators reported that fluazifop-butyl does not cause dominant lethal effects in CD-1 mice up to and including 287 mg/kg/day for 5 days. No toxicity demonstrated.
3. Other Genotoxicity	
Guideline 870.5395; *In vivo* mouse micronucleus test (1983) Acceptable Test material: [FB] and [FPB] Acceptable	In an *in vivo* mammalian cell mouse micronucleus assay (MRID# 0016244,92068014), C57BL/6J mice were administered FB or FPB at doses of 250 or 400 mg/kg and bone marrow removed after 24, 48 or 72 hours to determine the frequency of MPCEP. FB and FPB were tested up to 80% and 50% of the LD50 in mice. There were no adequate evidence of a positive response of increased micronuclei over background with either fluazifop-butyl [FB] or fluazifop-P-butyl [FPB] at toxic doses.

Table 4.1d:Reviewed/in Review Submitted Studies found to be unacceptable and/or did not affect the risk assessment.		
Studies included in this table after preliminary review were found: (1) to show effects at higher dose levels than studies included in Table 4.1b, (2) to show no effects that would alter the risk assessment, (3) to show unacceptable characteristics preventing use of the study results, or (4) to be for information purposes only.		
870.4200 Carcinogenicity (rats) with fluazifop acid metabolite	00093798 (1981) Unacceptable/guideline 0, 0.10, 0.30, 1.0 or 3.0 mg/kg /day	Unacceptable. Insufficient toxicity was shown.
870.4200b Carcinogenicity (mouse) with FB	41563702 (1983) Unacceptable/guideline 0, 1.0, 5.0, 20 or 80 ppm M: 0, 0.084, 0.42, 1.72 or 7.26 mg/kg/day F: 0, 0.089, 0.46, 1.83 or 7.11 mg/kg/day	Unacceptable. Insufficient toxicity was shown.
870.4200 Carcinogenicity (mouse) with fluazifop acid metabolite	00093799 (1983) Unacceptable/guideline 0, 0.10, 0.30, 1.0 or 3.0 mg/kg/day	Unacceptable. Insufficient toxicity was shown.

Table 4.1d:Reviewed/in Review Submitted Studies found to be unacceptable and/or did not affect the risk assessment.		
NG Developmental toxicity (Wistar rat) with FPB	46082915 (1990) Acceptable/NG Unacceptable for developmental toxicity study 0, 2.0, 5.0, 100 mg/kg/day dosed day 17-21 of gestation	Unacceptable because dams were dosed gestational day 17 - 21 instead of gestational days 6-16/21.
NG Range-finding Reproduction for the 2-generation study MRID# 00088859 FB	46082924 (1980) Acceptable/NG 0, 10, 30, 100, 300,1000 ppm	NOAEL/LOAEL not chosen Reproduction and fertility not affected. Birth body wt reduced at 1000 ppm [at 24 hr] and 96hours and 100 ppm. Pup Bwt decreased from control at 300 ppm, but not SS due to high std deviation. Body wt gain reduced at 100 & 1000 ppm at 96 hours postnatal measurement. Dose levels for 2-Gen study should be 10 to 300 ppm. Acceptable as a range-finding study/NG
NG Testes from 2-generation study with FB, MRID# 0008859, examined histologically	46082911, 46082917 (1985) Acceptable/NG Dose: 0, 10, 80, 250 ppm	Testes from the 2-generation study [0008859,92067050] were histologically examined. Testicular tubal length, size & some spermatogenic staging of the testes was estimated. No dose related testicular histopathology was seen in spermatid alignment at tubule lumen, spermatid with some specified abnormality or tubules classified as neither a or b and not VIII. No histological correlates were noted for the testes weight decrease seen in the 2-generation study. Tissue was stated to be normally processed, which generally means it was fixed in formalin, embedded in paraffin and stained with H&E. Testis tissue processed this way is generally unsuitable for staging spermatogenesis (difficult to identify many features). Thus, it is not surprising that no dose related effects were seen. The more sensitive sperm motility/morphology/live/dead counts were not done. Acceptable NG, but not acceptable for effects on sperm parameters.

Table 4.1d:Reviewed/in Review Submitted Studies found to be unacceptable and/or did not affect the risk assessment.		
NG Testes weight and histological studies with FB	46082920 (1986) Acceptable/NG 22-day study of testes weight Acceptable/NG, but does not adequately explain testes weight decrement Dose: 0, 20 or 100 mg/kg/day	Male rats treated (3 treatments/study types) with FB by gavage at 0, 20 and 100 mg/kg/day. (Study 1) 35 day old/5 rats/group treated for 4 days, (Study 2) 35 day old 10 rats/group treated for 9 days, (Study 3) 35 day old/23 rats/group treated for 22 days. Daily body wt determined of all rats, and brain, liver, epididymis, seminal vesical and prostate wt and testosterone, FSH and LH determined on all rats at end of dosing when they were sacrificed. (Study 3) showed body wt dec. at 20 and 100 mg/kg/day after 10 days. (Study 2) and (Study 3) showed liver wt incre. at 20 and 100 mg/kg/day and (Study 3) showed decreased seminal vesicle wt at 100 mg/kg/day. FSH decrease, statistically significant at day 4 with the 20 & 100 mg//kg/day doses. (Study 1) in rats and LH was decreased statistically at 100 mg/kg/day, (Study 3) rats, but all within normal variation. The only convincing effect was a liver wt incr at 20 & 100 mg/kg/day at day 1-9 (Study 2) & 1-22 (Study 3). Again measured sperm did not changed histologically. Statistically significant decrease in seminal vesicles wt at 100 mg/kg/day (Study 3) believed to decr fluids which were measured subjectively, only. Either the treatment periods were insufficiently long to showed testes wt decrement, or there is rat variation in susceptibility to testicular wt decrement or the testes wt decrement in the 2-gen study was incidental.
NG Human exposure form spraying with FB	00131455 (1983) Unacceptable/NG	Unacceptable because of ambiguities.
Not a study	46082922	Summary information, in review
NG Dermal absorption studies	46082926	Unacceptable because technical grade of a single pesticide was not used.
NG Dermal absorption studies	46082927 & 46082928	Literature reports with insufficient detail.

4.2 FQPA Hazard Considerations

4.2.1 Adequacy of the Toxicity Data Base

The Assessment team concluded that the toxicology database for fluazifop-butyl and fluazifop-P-butyl is complete for FQPA evaluation. Acceptable developmental toxicity studies in rats and rabbits on fluazifop-butyl and fluazifop-P-butyl are available in addition to an acceptable 2-generation reproduction study in rats. Studies on fluazifop-butyl may be used to support fluazifop-P-butyl due to equivalency in toxicity.

4.2.2 Evidence of Neurotoxicity

The Assessment team concluded that there was not a concern for neurotoxicity resulting from exposure to fluazifop-P-butyl at relevant exposure levels. There was no evidence of clinical signs indicative of neurotoxicity or neuropathology in the available studies. Marginal increases in brain weights at termination were seen in a subchronic toxicity study in a rats and a carcinogenicity study in hamsters, but only at high doses.

4.2.3 Developmental Toxicity Studies

4.2.3.1 Developmental Toxicity Study Conclusions

The data base included 7 developmental toxicity studies: 2 with fluazifop-butyl in Sprague-Dawley rats; 3 with fluazifop-P-butyl in Wistar rats; 1 with fluazifop-butyl in New Zealand rabbits; and 1 with fluazifop-P-butyl in New Zealand rabbits. These studies are summarized below:

The NOAEL/LOAEL in the five rat developmental toxicity studies was determined by a weight of evidence criteria mainly around consistency of delayed ossification, delayed development of the urinary tract, and diaphragmatic hernias. Although, delayed ossification was seen in some studies at lower doses, they were inconsistent (i.e., low incidence of delayed ossification in controls compared to historical controls, large variation in historical controls, the delayed ossification was not clearly dose related, and litter incidence was not statistically significant).

The LOAEL is 5.0 mg/kg/day based on decreased fetal weight and increased incidence of hydroureter in fetuses and litters, and delayed ossification in a 160 litter/group developmental toxicity study (MRID# 00088858). This LOAEL is also supported by a dose related increased fetal incidence in partially ossified sternebrae and sternebrae bipartite, 5th (MRID# 46082913, 46082903), and statistically significant increased incidence of fetuses and litters with interparietals, occipitals and parietals partially ossified, calcaneum not ossified and increased manus and pes scores at 5.0 mg/kg/day (MRID#46082903 and 46158401). The NOAEL of 1.0 mg/kg/day in the 160 litter per group study was not selected and a NOAEL of 2.0 mg/kg/day from the Wistar rat studies was selected. Since apparent effects noted at 0.05 and 1.0 mg/kg/day were either not dose related, concurrent controls were low, the effects were lower than the historical control range, or were not statistically significant in litters, and 2 developmental studies that included a 2 mg/kg/day dose group failed to elicit a dose dependant response, a NOAEL of 2.0 mg/kg/day was selected.

The overall rat studies showed a NOAEL/LOAEL of 2.0/5.0 mg/kg/day. The NOAEL/LOAEL was chosen from among MRID# 0008858, 46082903, 46082913 and 46518401. **For a single dose effect, the NOAEL/LOAELs are 50/200 mg/kg/day based on the diaphragmatic hernia malformations.**

The maternal toxicity NOAEL/LOAEL of 100/300 mg/kg/day was based a combination of factors. There was a clear effect on maternal weight decrement at 300 mg/kg/day in the Wistar rat studies and a clear NOAEL at 100 mg/kg/day in the Wistar rat studies. Although, the

maternal weight decrement in the Sprague Dawley rat was shown to be due to gravid uterine weight decrement, it was not completely clear that maternal toxicity was not expressed at 200 mg/kg/day. Therefore the maternal NOAEL was chosen among the three Wistar rat developmental toxicity studies to remove this ambiguity in maternal toxicity.

4.2.3.2 Fluazifop-butyl - Sprague Dawley Rats

In a developmental toxicity study (MRID# 00088857, 92067047 and 92067019), fluazifop-butyl, [PP009 (94.8% a.i., batch/lot # P14)] was administered to 22 female CD Sprague Dawley strain rats/group in a corn oil (2 ml/kg) gavage at dose levels of 0, 10, 50 or 200 mg/kg bw/day from days 6 through 20 of gestation. Animals were sacrificed on day 21 and uterine contents examined. Maternal body weights, food consumption, and liver weights were collected. Ovaries were examined for corpora lutea and uteri were examined for implantation sites. Fetuses were weighed and examined externally and viscerally by free serial sectioning by Wilson's method and approximately half of the fetuses were examined skeletally by the method of Dawson.

No maternal toxicity was seen at any dose level. **For maternal toxicity, the NOAEL was 200 mg/kg/day (HDT); a LOAEL was not established.**

Delayed fetal growth occurred in the form of fetal weight decrement (12%) at 200 mg/kg/day and delayed ossification was seen at all dose levels.

Various parameters significant to development were affected relative to concurrent and/or historical controls. Post implantation loss was increased (125%) at 200 mg/kg/day. Examination of the heads of fetuses showed increased large fontanelles at 200 and 50 mg/kg/day (45.9% and 11.9%, respectively, versus 3.4% in concurrent controls. Increased incomplete and/or irregular ossification of cranial sutures at 200 and 50 mg/kg/day (58.9% and 43.7%, respectively, versus 14.3% in concurrent controls. The incidence of fissures into the interparietal bone was increased at 200 mg/kg/day (2.2% versus 0% in concurrent and historical controls. Only the percentages of fetal anomalies were presented with no litter incidence. No statistical analysis was presented for the fetal anomalies.

Increased incidence of incomplete ossification of thoracic vertebral centra at 200, 50 and 10 mg/kg/day (75.5%, 58.7, 48.4, respectively, versus 38.5% in concurrent controls, with a historical control range of 0-70.3%) appeared to be test material related. An increased incidence of absent hyoid bone at 200 and 50 mg/kg/day (23.0% and 17.2% versus 10.8% in concurrent controls) was observed. Increased incidence of incomplete ossification of one or more pelvic bones at 200 and 50 mg/kg/day (7.4% and 2.3%, respectively, versus 1.4% in concurrent control) was also observed. Absent hyoid bone and incomplete and/or irregular ossification of the cranial bones, and incomplete ossification of one or more pelvic bones may have been increased at 50 mg/kg/day, but since concurrent controls were higher than the mean historical control, these effects may have been incidental. The incidence of bilateral hydronephrosis at 200 mg/kg/day exceeded the historical control mean but not the range. The incidence of bilateral hydroureter at 200 mg/kg/day exceeded the historical control range and mean. No hydronephrosis nor hydroureter were seen in concurrent controls. In addition, subcutaneous edema (17.7% at 200 mg/kg/day versus 3.4% in concurrent controls) exceeded the mean of 8.9% in historical controls

(the upper range was unreadable). The concurrent controls also were less than the mean of historical controls.

Diaphragmatic hernia was seen in 1 fetus at 10 mg/kg/day, none at 50 mg/kg/day, and in 3 fetuses at 200 mg/kg/day, with no incidences in 2970 historical control fetuses. However a subsequent much larger study (MRID# 00088858) with 160 litter/group, showed an incidence of diaphragmatic hernias of 3/1113 in control fetuses, 1/1081 fetuses at 1 mg/kg/day, 3/1073 fetuses at 5 mg/kg/day, 2/1064 fetuses at 10 mg/kg/day, and a statistically significantly increased incidence in 59/1064 fetuses and 45/159 litters at 200 mg/kg/day. Since this anomaly was seen at a higher incidence (3 fetuses) in the controls in this study and was not replicated at the same dose in the second study, the single incidence of diaphragmatic hernia at 10 mg/kg/day was considered to be an aberration and not attributable to treatment.

For developmental toxicity, the LOAEL is 10 mg/kg/day based on incomplete and/or irregular ossification of the cranial bones and incomplete ossification of thoracic vertebral centra; a NOAEL was not established.

The developmental toxicity study in the rat is classified, **ACCEPTABLE (GUIDELINE)** and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rat.

4.2.3.3 Fluazifop-butyl - Sprague Dawley Rats

In a developmental toxicity study (MRID# 00088858, 92067048 and 92967020) [fluazifop-butyl, PP009 (94.8% a.i., batch/lot # P14)] was administered to 159 or 160 female CD Sprague Dawley strain rats/group in a corn oil (2 ml/kg) gavage at dose levels of 0, 1.0, 5.0, 10 or 200 mg/kg bw/day from day 6 through 20 of gestation. Animals were killed on day 21 and uterine contents examined. Maternal body weights, food consumption and uterine weights were collected. Ovaries were examined for corpora lutea, and uteri were examined for implantation sites. Fetuses were weighed and examined externally and viscerally at post mortem and by Wilson's free serial sectioning method and approximately half of the fetuses were skeletally examined by the method of Dawson.

Maternal body weight during gestation was slightly, but statistically significantly reduced (2%, $p < 0.01$) on day 21 at 200 mg/kg/day; dose related decreased gravid uterine weight at all dose levels accounted for all the decrease (4% at 1.0 mg/kg/day to 14% at 200 mg/kg/day). The gravid uterine weight that was reduced at all dose levels may be partly due to incidental reductions in amniotic fluid weight (mean number of implants and number of viable fetuses was not reduced at 1.0 or 5.0 mg/kg/day, placental weight was not reduced at 1.0, 5.0 or 10 mg/kg/day, and fetal weight was not reduced at 1.0 mg/kg/day. When corrected for gravid uterine weights, the body weights were comparable between treated and control groups. **For maternal toxicity, the NOAEL was 200 mg/kg/day (HDT); the LOAEL was equivocal.**

There were no differences in the number of corpora lutea, but implantations decreased (3% to 4%, $p<0.05$ to $p<0.01$) at 10 mg/kg/day and above. Viable young, resorptions, pre- and post implantation loss were all comparable with concurrent control and within historical control ranges. Fetal weight showed a dose related decrease at 5 mg/kg/day and greater (3% to 13%,

p<0.001 to p<0.001). The incidence of small fetuses less than 3.00 g in weight (mean control fetal weight was 3.60g±0.07) showed an increase at 200, 10 and 5 mg/kg/day (31.8%, 7.3%, 5.5%, respectively, versus 4.5% in concurrent control with a historical control mean of 3.7% and a range of 0-12.0%).

The delays in skeletal ossification such as incomplete ossification of thoracic and/or lumbar centra at ≥5 mg/kg/day are consistent with fetal weight decrement. Dose related incomplete ossification of one or more thoracic vertebral centra (54.5% versus 41.55 in control with a mean of 39.6% and a range of 15-70% in historical controls) and a dose related absent hyoid bone (15% versus 10% in controls with a mean of 7% and range of 0-23% in historical controls) were seen at ≥5 mg/kg/day. The absent hyoid bone may represent unossified hyoid or may have been miss-classified. Some of these delays in ossification were considered biologically significant at 10 mg/kg/day and 200 mg/kg/day, only.

Total hydroureter (free hand sectioning and post mortem) was significantly increased in litters at 5 mg/kg/day and greater (56%-81% versus 40.0% in concurrent controls) and in fetuses (8.2 - 19% versus 4.5% in concurrent controls with 5.9% in historical controls).

Diaphragmatic hernia (free hand sectioning and post mortem) showed an increased incidence in fetuses (5% versus 0.13% in control) and litters (43.4% versus 1.9%) at 200 mg/kg/day. In addition to the diaphragmatic hernias other anomalies were seen at 200 mg/kg/day, such as kidney and ureter anomalies, ectopic testes, head anomalies, incomplete and reduced ossification.

No statistical analysis was conducted on fetal anomalies other than hydroureter and diaphragmatic hernia. However, the study authors acknowledged the incidence of delayed ossification in the hyoid bone, thoracic and vertebral centra was increased at 5 and 10 mg/kg/day as well as 200 mg/kg/day.

For developmental toxicity, the NOAEL is 1 mg/kg/day and the LOAEL is 5 mg/kg/day based on delays in skeletal ossifications such as incomplete ossification of thoracic and/or lumbar centra and fetal weight decrements.

The developmental toxicity study in the rat is classified **ACCEPTABLE (GUIDELINE)**; and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rat.

4.2.3.4 Fluazifop-P-butyl - Wistar Rats

In a developmental toxicity study (MRID 46028903) [Fluazifop-p-butyl, calculated as 90.9% a.i.; batch/lot# BX 247T A10209)] was administered to [(24 females) Alderly Park strain of Wistar rats] rats/dose by gavage at dose levels of 0, 2, 5 or 100 mg a.i./kg bw/day from days 7 through 21 of gestation.

No maternal toxicity was seen. The statistically significant decrement in food consumption seen between gestational days 16 and 19 was not treatment related. Food efficiency and clinical observations showed no were treatment related response. **For maternal**

toxicity, the NOAEL is 100 mg/kg/day (HDT); a LOAEL is not established.

Delayed ossification was seen in skull bones. The incidence of the partially ossified occipital (3.3% to 7.1% versus 0% in control), interparietals (9.5% to 29.5% versus 0.4% in control, historical controls), and in parietal bones (14.2% to 38.2% versus 0.4% in control) were dose related and statistically significant in fetuses and litters at 5.0 mg/kg/day and above. [In this study, historical control data are useful but limited because it was collected on studies with dosing gestational day 7 - 16.]

The mean manus [10% to 30% of control] and pes scores [4% to 14% of control] showed a statistically significant dose related increase delayed ossification, starting at 5 mg/kg/day. [Manus and pes scores (1-6) were a subjective index of delayed ossification (1-6) in the fore paws and hind paws of each fetus.]

Other indications of delayed ossification were seen at the highest dose tested for cervical vertebral arches and centrum (not ossified) and sternebrae 5 and 6. In addition, the odontoid [tooth related] and calcaneum [heel bone] were not ossified at 100 mg/kg/day.

Fetal weight was significantly decreased 7% at 100 mg/kg/day only. Increased incidence of dilated ureter was seen only in litters at 100 mg/kg/day and kinked ureter in was dose related and statistically significant at all doses in fetuses, but not in litters at any dose level. There were no incidences of diaphragmatic hernias seen in this study.

For developmental toxicity, the NOAEL is 2.0 mg/kg/day and the LOAEL is 5.0 mg/kg/day based on dose related delayed ossification in skull bones [occipital and parietal] in fetuses and litters.

The developmental toxicity study in the rat is classified **ACCEPTABLE [guideline]**; and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rat.

4.2.3.5 Fluazifop-P-butyl - Wistar Rats.

In a developmental toxicity study (MRID 46082913; referred to as RR0491; 25/41 Part II, page 112/181 to 181/181)[Fluazifop-p-butyl, calculated as 90.3% a.i.; batch/lot# P12; CTL Ref.# Y02746/021] was administered to [(24 females) Alderly Park strain of Wistar rats (Alpk:APfSD)] rats/dose level by gavage at dose levels of 0, 2.0, 5.0 or 100 mg a.i./kg bw/day from days 7 through 16 of gestation.

No evidence of maternal toxicity was seen at any dose level. **For maternal toxicity, the NOAEL is 100 mg/kg bw/day (HDT); a LOAEL is not established.**

Delayed ossification was seen at 100 mg/kg/day in skull bones, which may have been dose related at 5 mg/kg/day. The parietal bones showed dose related statistically significant increased incidence of partial ossification in fetuses at 5.0 mg/kg/day and above [5.0% versus control 0%]. Partially ossified interparietals were nominally elevated at all dose levels, but showed a statistically significant dose related increased incidence at 100 mg/kg/day. At 5 and

100 mg/kg/day, partial ossification of skull bones exceeded the historical controls.

The mean manus score showed a statistically significant dose related increase (8%), starting at 5 mg/kg/day. Pes score were increased at 100 mg/kg/day. Manus and pes scores (1-6) were a subjective index of delayed ossification (1-6) in the fore paws and hind paws of each fetus.

Other delayed ossifications of concern were sternebrae bipartite and sternebrae partially ossified and calcaneum not ossified. The combination of sternebrae 5 bipartite and partially ossified showed a apparent increased incidence in fetuses at all dose levels, but an increased litter incidence at 5 mg/kg/day and above. The calcaneum not ossified showed a dose related and statistically significant increase in fetuses and litters at 5 mg/kg/day and above. Other indications of delayed ossification were seen at the highest dose tested for cervical vertebral arches and centrum (not ossified).

Fetal weight was significantly decreased 7% at 100 mg/kg/day only. Increased incidence of dilated ureter was seen only in litters at 100 mg/kg/day and kinked ureter in was treatment related and statistically significant in fetuses and litters at 100 mg/kg/day. There were no incidences of diaphragmatic hernias seen in this study.

For developmental toxicity, the NOAEL is 2.0 mg/kg/day and the LOAEL is 5.0 mg/kg/day, based on dose related delayed ossification in skull bones [parietal], sternebrae bipartite, sternebrae partially ossified and calcaneum not ossified in fetuses and litters.

The developmental toxicity study in the rat is classified **ACCEPTABLE [guideline]**; and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rat.

4.2.3.6 Fluazifop-P-butyl - Wistar Rats

In a developmental toxicity study (MRID 46158401)[Fluazifop-p-butyl, calculated as 90.1% a.i.; batch/lot# P12; CTL Ref.# Y02746/021/003] was administered to [(24 females) Alderly Park strain of Wistar rats] rats/dose by gavage at dose levels of 0, 0.5, 1.0, 20, or 300 mg a.i./kg bw/day from days 7 through 16 of gestation.

Maternal toxicity at 300 mg/kg/day was indicated by a body weight gain decrement of 19% during the dosing period, GD 7-16. Food consumption was decreased statistically significantly at the same dose and food efficiency decreased 13%. **For maternal toxicity, the NOAEL is 20 mg/kg/day and the LOAEL is 300 mg/kg/day based on decreases in body weight gain maternal animals.**

Developmental effects were shown by delayed ossification in many parameters at ≥20 mg/kg/day. The incidence of parietals partially ossified were statistically significant and dose related in fetuses and litters at 20 mg/kg/day. The statistically significant increase in interparietals partially ossified in fetuses at 20 mg/kg/day exceeded historical controls and support the delayed ossification of the parietal bones. Cervical vertebral arches 4 and 5 partially ossified and centrum (4^{th} not ossified) at 20 mg/kg/day showed statistically significantly

increased incidence in fetuses and litters. Manus Scores were statistically significantly increased at 1.0, 20, and 300 mg/kg/day. Pes score were statistically significantly increased at 20 and 300 mg/kg/day.

The other delayed development at 1.0 and 0.5 mg/kg/day either were not dose related, were less than historical controls or showed no treatment related effects in litters. The slightly increased manus scores at 1.0 mg/kg/day were not supported by the previous 0-100 mg/kg/day (dose GD 6-16; MRID# 46082913) study nor by another study dosed 0-100 mg/kg/day on gestational day 7-21 (MRID# 46082903). Neither study showed statistically significant manus scores at 2.0 mg/kg/day. [Manus and pes scores (1-6) were a subjective mean index of delayed ossification (1-6) in the fore paws and hind paws of each fetus.] Other indications of delayed ossification were seen in fetuses and litters at 300 mg/kg/day, the highest dose tested.
Fetal weight was significantly decreased 14% at 300 mg/kg/day and 2% at 20 mg/kg/day.
Increased incidence of kinked ureter was seen at all doses, but reached statistically significance at 300 mg/kg/day. There were no incidences of diaphragmatic hernias seen in this study.

For developmental toxicity, the NOAEL is 1.0 mg/kg/day and the LOAEL is 20 mg/kg/day based on dose related delayed ossification in skull bones [parietal], delayed ossification of the cervical arches and centrum (not ossified) in fetuses and litters and delayed ossification of the manus and pes.

The developmental toxicity study in the rat is classified **ACCEPTABLE [guideline]**; and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rat.

4.2.3.7 Fluazifop-butyl - Rabbit

In a developmental toxicity study (MRID 00088856, 92067049 and 92067021) [fluazifop-butyl, PP009 (94.8% a.i., batch/lot #) P14] was administered to 20-24 New Zealand White female rabbits/dose in a corn oil gavage at dose levels of 0, 10, 30 or 90 mg PP009/kg bw/day from day 6 through 28 of gestation. Maternal weight data, implantations, and fetal data were evaluated.

Clinical observations revealed no consistent differences between treated animals and control animals, other than abortions and possibly gastrointestinal distress and respiratory distress at 90 mg/kg/day. At 90 mg/kg/day, 2 had respiratory distress and 4 had gastrointestinal distress. These deaths occurred from day 2 to day 28 (1 at day 2 and 1 day 8, the remaining after day 14). At 90 mg/kg/day of the animals that died or were killed, 4 animal showed gastrointestinal tract disorders from intestinal gas to stomach ulceration and 2 showed respiratory distress. This reviewer believes that the test material exacerbated the severity of the respiratory distress as well as the gastrointestinal tract disorders, resulting in death in the 90 mg/kg/day group, but the authors did not believe the deaths were test material related.

Body weight was comparable with control values through out the study. Food and water consumption in treated groups was comparable with control values. A nominal absolute liver (13%) and relative liver weight (9%) increase was seen at 90 mg/kg/day.

A treatment related increase in abortions was seen in the study. From control to 90 mg/kg/day, 3, 1, 2 and 7, respectively, abortions occurred from day 21 through day 29. The dams with abortions showed no decrease in corpora lutea or implantation sites. Five of the 7 dams aborting had all of their implants resorbing, suggesting that death of the fetus may have been implicated in the abortion. One totally resorbed litter was seen in 1 control animal not aborting.

For maternal toxicity, the NOAEL is 30 mg/kg/day and the LOAEL is 90 mg/kg/day based on abortions.

No statistically significant fetal effects were shown in the study, however, several nominally increased fetal effects were noted at 90 mg/kg/day. A weight of evidence analysis shows that the fetus was affected at 90 mg/kg/day. Abortion with total litter loss was increased (43.8% versus 25.0% in control) at 90 mg/kg/day. Cloudy eyes were seen in the 90 mg/kg/day group (12.7% verus 0 in control). Although one fetus from1 litter showed cloudy eye(s) at 30 mg/kg/day (0.9%) with 0% in concurrent control, subsequent historical control data showed 2.2% incidence of cloudy eye(s). Gall bladder variants (not otherwise specified) were increased at 90 mg/kg/day (43.7% versus 34.4% in control with 42.7% maximum in historical controls). The incidence of small fetuses less the 32 g were nominally increased in the 90 mg/kg/day group (22.5% versus 12.9% in controls with a mean of 14.5% and a range of 0 to 30.4% in historical controls). Incompletely ossified hind limb long bone was increased (38% versus 9.7% in control with a maximum of 45.6% in historical controls) at 90 mg/kg/day. Absent tarsals and pubic bones were increased at 90 mg/kg/day (1.4% versus 0 in control with none seen in historical control data). Incompletely ossified hyoid bone was increased (16.9% versus 2.2% in control with a mean of 3.5% and a maximum historical control of 20.7%).

Other skeletal variations were increased over control, but control was either increased over the historical control range or increased over the mean of the historical control range, such as enlarged cranial sutures, enlarged posterior fontanelles, reduced/ misshapened/irregularly ossified interparietal bones.

Contributing to the weight of evidence for fetal effects at 90 mg/kg/day is an apparent treatment relationship with various anomalies and that the increased level in concurrent controls over historical controls is always accompanied by even higher levels of the anomaly at 90 mg/kg/day than in concurrent controls. Even though, none of the fetal effects were statistically significant, the weight of evidence would suggest that the fetus was affected at 90 mg/kg/day. Post implantation loss was increased (16.5% versus 5.1% in control with a mean of 11.1% and a maximum historical control range of 27.2%) at 90 mg/kg/day.

For developmental toxicity, the NOAEL is 30 mg/kg/day and the developmental LOAEL is 90 mg/kg bw/day based on a weight of the evidence including nominal increases in delayed ossification, total litter loss through death and abortions with total litter loss, small fetuses, cloudy eyes and possible post implantation loss, all of which were above the mean and/or the range in historical control data.

The developmental NOAEL/LOAEL indicated above differs from the values established in the original DER (TXR No.001852) since the effects seen at the 30 mg/kg/day (nominal

increase in small fetuses of 15.7%) was not considered to be adverse since the small fetuses were not significantly increased (22.5%) even at 90 mg/kg/day; the incidences were 12.5% in the concurrent controls and ranged from 1 to 30.5% among historical controls (MRID# 00088856, 92067049).

The developmental toxicity study in the rabbit is classified **ACCEPTABLE (GUIDELINE)**; and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rabbit.

4.2.3.8 Fluazifop-P-butyl - Rabbit

In a developmental toxicity study [MRID 46082904] [fluazifop-p-butyl (90.1% a.i., batch/lot # P12)] was administered to [(20 females) New Zealand White] rabbits/group by gavage in corn oil vehicle [1 ml/kg] at dose levels of 0, 2, 10 or 50 mg a.i./kg bw/day from days 8 through 20 of gestation. Day sperm was found was designated as day 1. On day 30 of gestation, dams were killed and the uterine contents examined for live and dead fetuses. Fetuses were weighed, examined for external and visceral abnormalities, sexed, eviscerated and stained for skeletal examination.

Minimal maternal toxicity was shown by body weight loss and inappetance at 50 mg/kg/day among 3/4 dams that aborted and one dam that showed extreme body weight loss and inappetance and was killed on day 14. The aborted fetuses were alive. The abortions were uniformly distributed among groups and were not dose related, however, the abortion occurring at lower doses and in the control group were not preceded by body weight loss. No difference for controls in body weight or weight gain were seen among the surviving rabbits in the study.

For maternal toxicity, the NOAEL is 10 mg/kg/day and the LOAEL is 50 mg/kg/day based on death, abortions and body weight loss in dams.

Treatment related effects on development were seen in the 50 mg/kg/day group only. Statistically significant extra 13th rib and delayed ossification was seen in sternebrae 2 and 5. An increase in partially ossified 5 sternebrae was seen at 10 mg/kg/day, but the litter incidence was not increased. A nominal increase in malformations were seen at 50 mg/kg/day, such as acephaly [1 fetus/1 litter], cebocephaly [1 fetus/1 litter], cleft palate [1 fetus/1 litter], microphthalmia [1 fetus/1 litter], gastroschisis [1 fetus/1 litter], and multiple anomalies in 1 fetus/1 litter. None were duplicated and all could have occurred 1 to 3 times in the same litter, with 0 in control. Since individual animal data was not submitted, this incidence in litters could not be verified.

For developmental toxicity, the NOAEL is 10 mg/kg/day and the LOAEL is 50 mg/kg/day based on increased 13th rib and increased incidence of delayed ossification of sternebrae 2 and 5.

The developmental toxicity study in the rabbit is classified **ACCEPTABLE** (guideline) and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rabbit.

4.2.4 Reproductive Toxicity Study

In a 2-generation reproduction study (MRID 92067050, update of 00088859) [fluazifop-butyl, 94.8% a.i., batch/lot P14] was administered to 15 male Wistar rats and 30 female Wistar rats per group in the diet at dose levels of 0, 10, 80, 250 ppm (equivalent to a chemical consumption of 0, 0.74, 5.8, 17.5 mg/kg bw/day for males and 0, 0.88, 7.1, 21.7 mg/kg-bw/day for females) for 2 generations. Dosing was continuous for the P0 (100 days) generation and F1 (120 days) generation and to weaning of the F2 generation. Mating was 1 male to 2 females. Each female of the P0 and F1 generations was allowed to produce one litter. Estrous cycles were determined prior to the P0 and F1 matings. Pre-coital interval, mating index, pregnancy index, fertility index and gestation index were determined. All live pups were allowed survive to the end of lactation, i.e., no pup reduction to 8/litter at lactational day 4. P0 animals were subjected to gross necropsy, but only the male reproductive organs were weighed and subjected to histological examination. P0 females were examined for implantation sites and discarded. Ten F1 adults per sex per group were subjected to gross necropsy and complete histological examination. Five f1 and f2 weanlings per sex per group were subjected to gross necropsy and complete histological examination.

Clinical observations were unremarkable. Body weight of P0 and F1 adult males were unaffected by treatment at any dose. However, a nominal body weight increase was noted in both generations of males at 250 ppm during treatment. Body weight of P0 and F1 adult females were significantly increased (7% and 10%, respectively) only just prior to sacrifice, week 14 and week 17, respectively. No significant dose related changes in food consumption or efficiency were noted during the study. Water intake was not affected in either generation. The length of gestation was slightly, but significantly increased from 22.8 to 23.2 days for the P0 and from 22.6 to 23.1 days for the F1 parturition at 250 ppm. The F1 gestation length was also statistically significantly increased at 80 ppm (from 22.6 to 22.8 days), but the increase may not have been biologically significant. Estrous cycles were similar in all groups of P0 and F1 females and showed normal 4-5 day cycles.

The body weight increases in females may have been incidental or related to the significant absolute and relative increased kidney weight and slight increase in geriatric nephropathy found at termination at 250 ppm.

Signs of systemic toxicity were seen in organ weight changes in F1 adult males and females at the top dose and less frequently at the 2 top doses. In F1 adult males, absolute (18%) and relative (17%) liver weights were statistically significantly increased at 250 ppm and absolute (17%-18%) and relative (17.6%-17.6%) spleen weight were decreased at 80-250 ppm, respectively. Absolute (21%) and relative (13%) liver weights and absolute (15%) and relative (7%) kidney weights were also significantly increased in F1 adult females at 250 ppm. In F1 adult females, absolute and relative spleen weights were nominally decreased at 80 and 250 ppm, but neither were considered to be biologically significant. Spleen, liver, kidney, pituitary, uterine, ovarian weights were not measure in P0 males or females.

For parental/systemic toxicity, the NOAEL is 0.74 mg/kg/day in males and 7.1 mg/kg/day in females. The LOAEL is 5.8 mg/kg/day in males based on decreased spleen weight and 21.7 mg/kg/day in females based on increase absolute and relative liver and

kidney weights and geriatric nephropathy.

The number of live f1 (16% to 28%) and f2 pups (18 to 27%) were significantly decreased at day 1, 4, 11, 18 and 25 of lactation at 250 ppm. Implantation sites were significantly decreased in P0 females (8%) and nominally in F1 females (4.6%) at 250 ppm, only. F1 pup weights were not significantly affected at any dose level, but f2 pups (19%) showed significantly reduced weight at 250 ppm on lactational day 25, only. Hydronephrosis was increased in f1and f2 pups at 250 ppm. Pinnea unfolding, hair growth, eye opening, auditory response and visual response were comparable in all groups of f1 offspring, the only groups tested. Tooth eruption may have been marginally delayed.

For offspring toxicity, the NOAEL is 7.1 mg/kg/day and the LOAEL is 21.7 mg/bw/day based on decreased viability of F1 and F2 pups during lactational day 1, 4, 11, 18 and 25 and decreases in F2 pup weight on lactational day 25.

Most of the absolute and relative testes and epididymal weight decreases were significant in the P0 and F1 adults at 80 and 250 ppm. In P0 adults these organs were decreased (testes weights; absolute 7.7-8.3% and relative13%-13% and absolute epididymal weights; 9%-10% and rel.12%-12%). Absolute and relative testes weights were decreased in F1 adults at 80 ppm and 250 ppm (abs. 14%-14% and rel. 18%-16%). Absolute (8%-12%) and relative (9%-14%) epididymal weights were decreased in the F1 generation at 80-250 ppm, respectively. Slight pathology was shown in the testes of F1 adults. Slight atrophy of the germinal epithelium and/or seminiferous tubules were seen at histological examination in the P0 generation 2/13 and in the F1 adults 5/15 at 250 ppm, respectively. Correlated with these findings were decreased female pregnancy and fertility index in the F1 generation, but not in the male fertility index or male or female fertility index in the P0 generation.

Although some of the depressions in testes and epididymal weights in P0 and F1 males did not show a good dose related response, the consistency between generations and dose groups and the statistically significant tends show a treatment relationship.

F1 adult females showed an absolute (28%) and relative (18%) statistically significant increase in ovarian weight at 250 ppm. In F1 adult females, absolute pituitary weights (13%-20%) and uterine weights (18%-25%) were statistically significantly reduced at 80-250 ppm. Relative pituitary weights (18%-27%) and uterine weights (19%-29%) were reduced in F1 adult females at 80-250 ppm.

For reproductive toxicity, the NOAEL is 0.74 mg/kg/day in males and 0.88 mg/kg/day in females. The LOAEL is 5.8 mg/bw/day in males based on decreases in absolute and relative testes and epididymal weights and 7.1 mg/kg/day in females based on decreases in absolute and relative pituitary and uterine weights.

The NOAEL/LOAEL indicated above differs from the values established in the DER (TXR# 0001852) and reviewed by the RfD Committee in 1996 (TXR# 011840). The difference is due to the re-evaluation and interpretation of the study results.

This study is **ACCEPTABLE (GUIDELINE)**; and satisfies the guideline requirement

for a 2-generation reproductive study (OPPTS 870.3800); OECD 416 in rats.

4.2.5 Additional Information from Literature Sources

A literature search found several studies related to fluazifop toxicity. Several were combinations of studies submitted in greater detail to the Agency, including human excretion studies and studies on peroxasome proliferation in the rat, mouse and hamster (Kemal & Casida, 1992; Kostka et al., 2002; O'Brien et al., 2001). *In vitro* and *in vivo* skin permeability studies in the rat, human and pig were found, which yield some information about the low skin permeability of fluazifop-butyl (Dick & Scott, 1992)(Ramsey et al, 1992 and 1994). However, the published data included only summary data and lacked experimental detail and individual animal data to verify the summary data.

4.2.6 Pre-and/or Postnatal Toxicity

The Assessment team concluded that there is concern for pre/post-natal toxicity resulting from exposure to fluazifop-butyl and fluazifop-P-butyl.

4.2.6.1 Determination of Susceptibility

There was quantitative evidence of increased susceptibility in the fetuses of rats exposed *in utero* to fluazifop-butyl and fluazifop-P-butyl. Developmental toxicity characterized as delays in skeletal ossifications was seen in the absence of maternal toxicity consistently in two strains of rats. There was no evidence (quantitative or qualitative) of increased susceptibility following *in utero* exposures to rabbits or following pre-and/or post-natal toxicity in the two generation reproduction toxicity study in rats

4.2.6.2 Degree of Concern Analysis and Residual Uncertainties for Pre and/or Post-natal Susceptibility

The degree of concern is low for the increased susceptibility seen in the rats based on the following considerations: the endpoint of concern (delayed ossifications) is considered to be a developmental delay as opposed to a malformation or variation which is considered to be more serious in nature; there were considerable variations in the incidences among the five studies; the NOAELs/LOAELs for this effect were well defined and consistent across these studies; and a developmental endpoint of concern (diaphragmatic hernia) is used for assessing acute dietary risk. Therefore, there is no residual uncertainty for pre and/or post natal toxicity.

4.2.6.3 Special FQPA Safety Factor(s)

Based on the above-discussed data, there is no need for a special FQPA safety factor (i.e., 1X) since there are no residual uncertainties for pre-and/or post-natal toxicity..

The Special FQPA Safety Factor recommended by the Agency **assumes** that the exposure databases (dietary food, drinking water, and residential) are complete and that the risk assessment for each potential exposure scenario includes all metabolites and/or degradates of concern and does not underestimate the potential risk for infants and children.

4.3 Recommendation for a Developmental Neurotoxicity Study

4.3.1 Evidence that supports requiring a DNT study

- Slight increases in absolute and relative brain weights (2.5% in males and 1.6% in females) were seen at 3000 ppm (approximately 194 mg/kg/day) at termination in the carcinogenicity study in hamsters.

- Slight increases in brain weights were seen in female rats (2.9%) at 100 mg/kg/day and at 120 mg/kg/day in male hamsters (4%) after subchronic exposures with fluazifop-P-butyl.

4.3.2 Evidence that supports not requiring for a DNT study

- No developmental or central nervous system malformations were seen in any of the developmental toxicity studies with rats or rabbits.

- No evidence of neurotoxicity or neuropathology in adult animals in the available studies.

- The toxicological significance of the marginal increases in brain weights at high doses is unknown in the absence of corroborative histopathological lesions.

4.3.3 Rationale for No UF_{DB}

The Assessment team concluded that there is not a concern for developmental neurotoxicity resulting from exposure to fluazifop-butyl or fluazifop-P-butyl. The toxicology database is adequate for hazard characterization and endpoint selection. Therefore, no database uncertainty factors are needed for any database deficiencies.

4.4 Hazard Identification and Toxicity Endpoint Selection

4.4.1 Acute Reference Dose (aRfD) - Females age 13-49

In a developmental toxicity study (MRID 00088857), fluazifop-butyl was administered to 22 female CD Sprague Dawley strain rats/group in a corn oil (2 ml/kg) gavage at dose levels of 0, 10, 50 or 200 mg/kg bw/day from days 6 through 20 of gestation. Diaphragmatic hernia was seen in 1 fetus at 10 mg/kg/day, none at 50 mg/kg/day and in 3 fetuses at 200 mg/kg/day. No diaphragmatic hernia was seen in 2970 historical control fetuses. In a subsequent study (discussed below) with a larger number of litters (160 litter/group) diaphragmatic hernias were seen in 3 of 1113 control fetuses, 1 of 1081 fetuses at 1 mg/kg/day, 3 of 1073 fetuses at 5 mg/kg/day, 2 of 1064 fetuses at 10 mg/kg/day and in 59 of 1064 fetuses (and 45/159 litters)at

200 mg/kg/day. Since this anomaly was seen at a higher incidence (3 fetuses) in the controls in this study and was not replicated at the same dose in the second study, the single incidence of diaphragmatic hernia at 10 mg/kg/day was considered to be an aberration and not attributable to treatment.

In an another developmental toxicity study (MRID# 00088858) fluazifop-butyl was administered to 159 or 160 female CD Sprague Dawley strain rats/group in a corn oil (2 ml/kg) gavage at dose levels of 0, 1.0, 5.0, 10 or 200 mg/kg bw/day from day 6 through 20 of gestation. There was an increased incidence of diaphragmatic hernia were seen in fetuses (5% versus 0.13% in control) and litters (43.4% versus 1.9%) at 200 mg/kg/day.

Dose and Endpoint for Establishing aRfD: NOAEL is 50 mg/kg/day based on the increased incidence of diaphragmatic hernia at 200 mg/kg/day.

Uncertainty Factor (UF): 100. This includes 10X for inter-species extrapolation and 10X for intra-species variation.

Comments about Study/Endpoint/Uncertainty Factor: The NOAEL selected is based on the combined results of the two studies. In the two studies conducted in the same strain of rats with an identical dosing regimen, diaphragmatic hernias were seen at 200 mg/kg/day in both studies; none were seen at 50 mg/kg/day in the second study (MRID 00088858); and a single incidence was seen at 10 mg/kg/day in the first study (MRID 00088857). The single incidence in the first study was not considered to be treatment-related since the incidence was lower than that seen in the control fetuses in the second study and was not replicated at the same dose in the later study. Therefore, based on the combined doses tested, 0, 1, 5, 10, 50, or 200 mg/kg/day, for this effect, the NOAEL is 50 mg/kg/day and the LOAEL is 200 mg/kg/day. These values differ from the study NOAEL/LOAEL. This particular developmental effect is presumed to occur after a single exposure and thus is appropriate for this population subgroup (Females 13-49).

Acute RfD (Female 13- 49) = $\frac{50 \text{ mg/kg (NOAEL)}}{100 \text{ (UF)}}$ = **0.50 mg/kg**

4.4.2
Acute Reference Dose (aRfD) - General Population

An appropriate endpoint attributable to a single dose was not available in the database including the developmental toxicity studies.

4.4.3 Chronic Reference Dose (cRfD)

See Section 4.2.4 for a descriptive summary of the Two-Generation Reproduction Study in rats (MRID# 00008859, 92067022 & 92067050).

Dose and Endpoint for Establishing cRfD: NOAEL is 0.74 mg/kg/day based on decreases

in absolute and relative testes and epididymal weights in males at 5.8 mg/kg/day (LOAEL).

Uncertainty Factor(s): 100X (10X for inter species extrapolation and 10X for intra species variation.

Comments about Study/Endpoint/Uncertainty Factor: The study/dose/endpoint is appropriate for the route (oral) and duration (chronic) of concern. Although the endpoint of concern in based on male reproductive effects, decreases in pituitary and uterine weights were seen in females at a comparable NOAEL (0.88 mg/kg/day) and LOAEL (7.1 mg/kg/day).

Chronic RfD = $\frac{\text{0.74 mg/kg/day (NOAEL)}}{\text{100 (UF)}}$ = **0.0074 mg/kg/day**

4.4.4 Short-Term Incidental Oral Exposure (1-30 days)

See Section 4.2.3 for a descriptive summary of the Developmental Toxicity Studies in rats (MRID# 46082913, 46158401, 46082903). A brief summary relevant to the endpoint selected is presented below.

In a developmental toxicity study (MRID# 46082913) fluazifop-P-butyl was administered to Aderly Park strain of Wistar rats by gavage at dose levels of 0, 2.0, 5.0 or 100 mg a.i./kgday from days 7 through 16 of gestation. No evidence of maternal toxicity was seen at any dose level. **For maternal toxicity, the NOAEL is 100 mg/kg/day (HDT); a LOAEL is not established.**

In another developmental toxicity study (MRID 46158401) fluazifop-P-butyl was administered to Alderly Park strain of Wistar rats by gavage at dose levels of 0, 0.5, 1.0, 20, or 300 mg/kg /day from days 7 through 16 of gestation. Maternal toxicity at 300 mg/kg/day was indicated by a body weight gain decrement of 19% during the dosing period, GD 7-16. Food consumption was decreased statistically significantly at the same dose and food efficiency decreased 13%. **For maternal toxicity, the NOAEL is 20 mg/kg/day and the LOAEL is 300 mg/kg/day based on decreases in body weight gain maternal animals.**

In yet another developmental toxicity study (MRID# 46028903) fluazifop-P-butyl was administered to Alderly Park strain of Wistar rats by gavage at dose levels of 0, 2, 5 or 100 mg a.i./kgday from days 7 through 21 of gestation. No maternal toxicity was seen. **For maternal toxicity, the NOAEL is 100 mg/kg/day (HDT); a LOAEL is not established.**

Dose and Endpoint for Risk Assessment: Maternal NOAEL of 100 mg/kg/day based on decreases in body weight gain in maternal animals during the dosing period (GD 7-16) at 300 mg/kg/day (LOAEL).

Comments about Study/Endpoint: The maternal NOAEL is selected based on the combined results of the two studies with support from the third study. The first two studies were

conducted in the same strain of rats (Wistar) with identical dosing regimen (dosing during GD 7-16) in the same laboratory. The lower NOAEL (20 mg/kg/day) in the second study (46158401) is an artifact of dose selection. Additionally, the NOAEL is supported by another study conducted in the same strain of rats with a slightly longer dosing period (GD 7-21) where no maternal toxicity was seen at 100 mg/kg/day, the highest dose tested (MRID# 46082903). This dose/endpoint is appropriate for the population (infants and children) and duration (1-30 days) of concern.

4.4.5 Intermediate-Term Incidental Oral Exposure (1-6 months)

See Section 4.2.4 for a descriptive summary of the Two-Generation Reproduction Study in rats (MRID# 00008859, 92067022 & 92067050).

Dose and Endpoint for Establishing cRfD: NOAEL is 0.74 mg/kg/day based on decreases in absolute and relative testes and epididymal weights in males at 5.8 mg/kg/day (LOAEL).

Comments about Study/Endpoint: The endpoint of concern was seen after approximately 13-16 weeks of exposure and thus is appropriate for the duration (1-6 months) of concern. Although the endpoint of concern in based on male reproductive effects, decreases in pituitary and uterine weights were seen in females at a comparable NOAEL (0.88 mg/kg/day) and LOAEL (7.1 mg/kg/day). These endpoints are appropriate for the population (infants and children) of concern.

4.4.6 Dermal Absorption

In a dermal absorption and pharmacokinetic study in humans (MRID# 46082918), six men (age 18-45; weight 60-90 kg)/dose were dosed dermally with 2 mg or 200 mg of 0.05% or a 5.0% (w/v) solution of fluazifop-butyl in a formulation. Four ml of each solution was spread over 800 cm^2 of the backs of 6 men/dose level, allowed to dry and left unoccluded for 8 hours. Plasma and urine was collected in multiple samples over a 264 hour period. Plasma was collected hourly for 4 hours, every 2 hours for 12 hours and every 24 hours to the end. Urines were collected every 4 hours for 12 hours and then every 24 hours to the end. After 8 hours, the application site was washed with water using cotton swabs and 3% Teepol and covered with a T-shirt over the application site until morning. At 24 hours after application the site was again washed with a 3% solution of Teepol. The washes, T-shirts, plasma and urine samples were analyzed for fluazifop-butyl or fluazifop acid.

Most of the applied dose appeared to be in the stratum corneum and easily removed. Recovery of test material was good, a mean of 93.4% ± a standard deviation of 13% at the 2 mg dose and mean of 83.2% ± a standard deviation of 21% at the 200 mg dose. Peak plasma levels were shown to occur 24 to 31 hours after application in these men. The one half life for excretion was about 18 hours. In arriving at these percentages of recovery, the study author's added a correction to the amount excreted in the urine up to 120 hours, i.e., to the amount excreted up to 120 hours was added the amount excreted after 120 hours through a 2 compartment pharmacokinetic model. However, this latter correction was insignificantly small

amounting about 0.008% of the 200 mg applied to the skin. In arriving at the dermal absorption percentage, the study author's corrected the recovery by three factors, 1.17 [the ratio of the mole weight fluazifop-butyl and fluazifop acid], 100/91 [the amount of recovery from thawed frozen urine (no supporting data was presented)] and 100/90 [the recovered urinary fluazifop acid from a oral study in humans (supported by MRID 00131464)]. This later factor was used to correct for residual material in organs and tissue, which would require similar test subjects in both studies for which there is not evidence. The study author's calculated the percentage absorption to be 8% at the 2 mg dose and 1.6% at the 200 mg dose.

The current reviewer modified the study author's percentage absorption. The modified dermal absorption was calculated by two methods; (1) Unrecovered added to absorbed material, and (2) Scaling recovered material to100%. Method (1) yielded absorption factors of 18.4% and 14.6% at the 2 mg dose and 200 mg dose, respectively. Method (2) yielded absorption factors of 8.6% and 1.9% at the 2 mg dose and 200 mg dose, respectively. Method (2) appeared to be more reasonable because residual material (unrecovered) may have been relatively immobile. The unrecovered test material was speculated to be in the outer layers of the skin and appeared to be easily removed.

Human oral studies with fluazifop-butyl show rapid excretion of fluazifop acid in the urine and almost no excretion in the feces of humans (MRID# 00131464). Oral dog and female rat studies show similar results, which were similar to human oral studies. Male rats show similar fluazifop acid excretion to the female, but excretion is slower because fluazifop is excreted in the bile, resulting in a higher % in the feces of males rats. Residual fluazifop acid appears to be retained in the body fat (<1% to 8% in the rat) and speculated to be esterified to mono or diglycerides. This small amount of residual material if released, was too low to be accurately detectable in the urine. Since multiple dosing studies show that fluazifop-butyl does not accumulate in the body and is not a carcinogen. This residual material is relatively immobile and may be toxicologically insignificant. Thus, the scaling of the recovered material to100% or method (2) may supply an appropriate dermal absorption factor. In conclusion, the dermal absorption factors are 8.6% and 1.9% for the dermal dose of 2 mg and 200 mg, respectively.

4.4.7 Short-Term Dermal Exposure (1-30 days)

See Sections 4.4.1 and 4.4.4 for a descriptive summary of the Developmental Toxicity Studies in rats (MRID# 00088858, 46082903, 46082913, 46158401). Though the Assessment team chose two short-term dermal endpoints, one for females of child-bearing age based on concerns for *in utero* effects, and another for all other population subgroups, for regulatory purposes, the dose and endpoint for the most sensitive population was used in the risk assessment for all population subgroups. Since females of child-bearing age cannot be excluded or treated separately from the general population should regulatory and/or mitigation measures be necessary, it is incumbent upon the Agency to address the potential risks of the most sensitive population as representative of the entire population.

The short-term dermal endpoint that the assessment team chose for the general population, including infants and children, was selected from 3 developmental toxicity studies in

rats (MRID# 46158401, 46082913 and 46082903). See a description under Section 4.4.4 Short-term Incidental Oral above. The dose/endpoint chosen is the maternal NOAEL of 100 mg/kg/day based on decreases in body weight gain in maternal animals during the dosing period (GD 7-16) at 300 mg/kg/day (LOAEL). For the reasons stated above, the risk assessment was conducted using the short-term dermal endpoint selected for females 13-49 years of age.

Dose and Endpoint for Risk Assessment: Developmental NOAEL is 2.0 mg/kg/day based on fetal weight decrement, increased incidence of hydroureter and delayed ossification at 5.0 mg/kg/day (LOAEL)

Comments about Study/Endpoint: The *in utero* effects are appropriate to assess dermal risks for the population subgroup, Females 13-49 from exposure to fluazifop-butyl. This endpoint was selected because of the developmental toxicity concerns seen consistently in rats and rabbits via the oral route. **The team did not select the 21-day dermal toxicity study in rabbits due to the concern for developmental toxicity which is not evaluated in the dermal study.** In addition, dermal study would not address the developmental concerns since the NOAEL (100 mg/kg/day) in that study is considerably higher than the dermal equivalent dose (22 mg/kg/day) obtained using the oral dose (2.0 mg/kg/day) with a 9% dermal absorption factor (2.0 ÷ 0.09 = 22).

Since an oral NOAEL was selected, an appropriate dermal absorption factor (i.e., 2% or 9%, exposure depended) was used for route-to-route extrapolation.

4.4.8 Intermediate and Long-Term Dermal Exposure (1-6 months & > 6 months)

See Section 4.2.4 for a descriptive summary of the Two-Generation Reproduction Study in rats (MRID# 00008859, 92067022 & 92067050).

Dose and Endpoint for Risk Assessment: NOAEL is 0.74 mg/kg/day based on decreases in absolute and relative testes and epididymal weights in males at 5.8 mg/kg/day (LOAEL).

Comments about Study/Endpoint: The endpoint of concern was seen after approximately 13-16 weeks of exposure and thus is appropriate for the duration (1-6 months) of concern. Although the endpoint of concern in based on male reproductive effects, decreases in pituitary and uterine weights were seen in females at a comparable NOAEL (0.88 mg/kg/day) and LOAEL (7.1 mg/kg/day). These endpoints are appropriate for the general population including infants and children. Since an oral NOAEL was selected an appropriate dermal absorption factor (i.e., 2% or 9%, exposure depended) was used for route-to-route extrapolation.

4.4.9 Short-Term Inhalation Exposure (1-30 days)

See Sections 4.4.1 and 4.4.4 for a descriptive summary of the Developmental Toxicity Studies in rats (MRID# 00088858, 46082903, 46082913, 46158401). Again, though the Assessment team chose two short-term inhalation endpoints, one for females of child-bearing age based on concerns for *in utero* effects, and another for all other population subgroups, for

regulatory purposes, the dose and endpoint for the most sensitive population was used in the risk assessment.

Dose and Endpoint for Risk Assessment: Developmental NOAEL is 2.0 mg/kg/day based on fetal weight decrement, increased incidence of hydroureter and delayed ossification at 5.0 mg/kg/day (LOAEL)

Comments about Study/Endpoint: The *in utero* effects are appropriate to assess inhalation risks for the population subgroup, Females 13-49 years from exposure to fluazifop-P-butyl. This endpoint was selected because of the developmental toxicity concerns seen consistently in rats and rabbits via the oral route. The Assessment team noted the absence of a repeated exposure inhalation toxicity study. For route-to-route extrapolation, absorption via the inhalation route is assumed to be equivalent to oral absorption.

4.4.10 Intermediate- and Long-Term Inhalation Exposure (1-6 months & > 6 months)

See Section 4.2.4 for a descriptive summary of the Two-Generation Reproduction Study in rats (MRID# 00008859, 92067022 & 92067050).

Dose and Endpoint for Risk Assessment: NOAEL is 0.74 mg/kg/day based on decreases in absolute and relative testes and epididymal weights in males at 5.8 mg/kg/day (LOAEL).

Comments about Study/Endpoint: The endpoint of concern was seen after approximately 13-16 weeks of exposure and thus is appropriate for the duration (1-6 months) of concern. Although the endpoint of concern is based on male reproductive effects, decreases in pituitary and uterine weights were seen in females at a comparable NOAEL (0.88 mg/kg/day) and LOAEL (7.1 mg/kg/day). These endpoints are appropriate for the general population including infants and children. Again, the Assessment team noted the absence of a repeated exposure inhalation toxicity study. For route-to-route extrapolation, absorption via the inhalation route is assumed to be equivalent to oral absorption.

4.4.11 HED's Levels of Concern (LOC)

Summary of HED's LOCs for risk assessment. MOEs that are less than the LOCs are of concern.

Route / Duration	Short-Term (1-30 Days)	Intermediate-Term (1 - 6 Months)	Long-Term (> 6 Months)
Occupational (Worker) Exposure			
Dermal	100	100	100
Inhalation	100	100	100

Residential (Non-Dietary) Exposure			
Oral	100	100	N/A
Dermal (All Populations)	100	100	100
Inhalation (All Populations)	100	100	100

For Occupational exposure: This is based on the conventional uncertainty factor of 100X (10X for interspecies extrapolation and 10X for intraspecies variation). Occupational exposure and risks are not being assessed at this time for this TRED.

For Residential exposure: This is based on the conventional uncertainty factor of 100X (1X for FQPA, 10X for interspecies extrapolation and 10X for intraspecies variation).

4.4.12 Recommendation for Aggregate Exposure Risk Assessments

As per FQPA, 1996, when there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. The fluazifop-P-butyl team chose to aggregate high-end exposures using conservative endpoints for a screening level assessment. If the resulting assessment showed risks of concern, further refinements would have been incorporated into the assessment but, it was not necessary. See section 7.0.

4.4.13 Classification of Carcinogenic Potential

The Assessment team, in accordance with the 1999 Draft Carcinogen Risk Assessment Guideline (April, 1999) classified fluazifop-butyl and fluazifop-P-butyl as "Not likely to be carcinogenic in humans," based on the lack of evidence of carcinogenicity in rats and hamsters. Progressive chronic nephropathy was observed in both rats and hamsters, but there was no statistically significant incidence of malignant and/or benign tumors seen at any dose in either study.

A carcinogenicity study in mice was not conducted. Peroxasome proliferation in the mouse was at levels much higher than in the hamster at comparable dose levels. Therefore, a carcinogenicity study in hamsters was conducted instead. The hamster was chosen because peroxasome proliferation *in vivo* and *in vitro* was more comparable to that found in human cell culture.

The Assessment team concluded that there is not a concern for mutagenicity resulting from exposure to fluazifop-P-butyl. The data base for mutagenicity is considered adequate based

on pre-1991 guidelines. No mutagenic potential was seen in adequately conducted pre-1991 guideline mutagenicity studies (*in vivo and in vitro*) on fluazifop-P-butyl or fluazifop-butyl. A structural analogue {haloxyfop-methyl [methyl 2-[4-[[3-chloro-5-(trifluromethyl)-2-pyridinyl] oxy]phenoxy]propinonate]} of fluazifop-P-butyl also showed no mutagenic potential.

4.4.13.1 Carcinogenic Potential in Rats

In a combined chronic/carcinogenicity study (MRID# 41563703) PP009 (fluazifop-butyl, 94.8% a.i., batch/lot # 14, Reference C4915, CTL Y00082/001/005)] was administered to [(60 Wistar rats/sex/group in the diet at dose levels of 0, 2, 10, 80 or 250 ppm (equivalent to 0, 0.10, 0.51, 4.15 or 12.29 mg/kg bw/day for males and 0.127, 0.65, 5.20 or 16.0 for females) for 106 or 107 days, respectively. Additional groups of 10 rats/sex/group were administered the test material in an analogous manner for 52 weeks prior to an interim sacrifice.

Clinical signs were characteristic of rats, except respiratory distress, nasal and ocular discharge were seen among some males at 80 and among some males and females at 250 ppm from week 29 to 55. These signs were accompanied by body weight loss and death in the seriously affected males at 80 and 250 ppm and in the seriously affected females at 250 ppm.

Body weight gain of males and females, not dying, were increased significantly up to week 28 at 80 (14% in males and 19% in females) and 250 ppm (10% in males and 20% in females) and in males week 29-44 at 250 ppm (26%), thereafter body weight gain was nominally increased in males at 10, 80 and 250 ppm and nominally increased in females from week 29-108 at 2, 10, 80 and 250 ppm. There was an overall nominal body weight gain increase in males and females at the three top dose levels for the 106 weeks of the study. However, male (-79 g to -123g versus -101 in control males) and female (-9 g to -24 g versus -24g in control females) rats lost body weight between week 81-85 and at the end of the study. No differences from control were seen in food consumption, food efficiency, water consumption or urinalysis among the groups.

There appeared to be a dose related increased mortality among males at 80 and 250 ppm (33% at 80 ppm and 34% at 250 ppm versus 14% in control) and among females (21% at 250 ppm versus 4% in control) during the first 52 weeks of the study. Overall mortality at cumulative termination appeared to be increased in males at 80 and 250 ppm (88%-86% versus 68% in control) and in females at 250 ppm (65% versus 45% in controls). The report stated that the death occurring up to week 52 was cause by respiratory problems exacerbated by test material related nephropathy (all grades) in nearly 100% of the affected males dying at 80 and 250 ppm and 87% of the affected females dying at 250 ppm. No dose related mortality was seen from week 52 to termination.

Dose related nephropathology, slight, moderate and marked, but not otherwise specified was seen in the animals dying or killed in extremis during the first 52 weeks of the study. This nephropathy was seen in control, 2, 10, 80 and 250 ppm group animals; 9/10, 9/9, 6/6, 22/23, and 24/24, respectively in males and 0/3, 0/1, 1/6, 1/ 2 and 13/15, respectively in females dying or killed in extremis. Treatment may have exacerbated the nephropathy. In animals sacrificed at

termination, geriatric nephropathy was seen in nearly all surviving animals [23/24 (96%) HDT versus 30/31 (97%) in control males] and [20/24 (83%) HDT versus 19/24 (79%) control females]. Gastrointestinal tract lesions appeared to be increased slightly at 250 ppm in males and females.

At ophthalmological examination, increased keratitis was seen in males (5/20) at 250 ppm. Since this observation was not seen in females and did not appear to be dose related at lower dose levels, the study authors questioned the toxicological significance of the finding.

Hematological parameters showed slight changes in males at 80 and 250 ppm. Decreased hematocrit (6-8%), hemoglobin concentration (3-4%) and erythrocyte count (6-8%) were slightly but statistically significant at week 12 and 25 and nominally decreased at week 78 at 80 ppm and 250 ppm. Hemosiderosis was found only in the spleens of one female each in control, 2 , 80 and 250 ppm groups. Blood chemistries showed increased cholesterol (about 85% to 107%) at various times of analyses up to 78 weeks in males and females, but not after 100 weeks in females at 250 ppm; males showed a nominal decrease in cholesterol after 100 weeks at the same dose. Albumin showed statistically significantly decreases of about 24% in males and females at 250 ppm.

Bone smears on males and female rats were similar to controls at week 52 or 106, but many smears in all groups could not be evaluated.

Decreased absolute (16%) and relative (17%) liver weights were statistically significant in males at 250 ppm at terminal sacrifice, and increased absolute (40%) and relative (37%) ovarian weights were significant at termination at 250 ppm; animals with ovarian cysts and masses were excluded from these calculations. Testes and seminal vesicle weight did not differ from control weight at terminal sacrifice, but were nominally decreased at 250 ppm. At the 52 week interim sacrifice, absolute and relative kidney (Abs. 29%) and thyroid (Abs. 33%) weights were significantly increased in males, but not in females at 250 ppm. Absolute (31%) and relative (24%) testes weight showed a treatment related decrease at 250 ppm at the 52 week sacrifice. Ovarian weights were nominally increased at 250 ppm and 52 weeks. Ovaries, possibly enlarged by cysts, appeared to have an increased incidence in the 250 ppm group than in control.

The LOAEL in males is 80 ppm (4.15 mg/kg/day) based on increased mortality and nephropathy from start to week 52 of the study. The NOAEL is 10 ppm (0.51 mg/kg/day in males). The LOAEL in females is 250 ppm (16.0 mg/kg/day) based on increased morality and nephropathy during the first 52 weeks of the study and increased ovarian weight and ovarian cysts at termination. The NOAEL was 80 ppm (5.2 mg/kg/day) for females.

At the doses tested, there was no treatment related increase in tumor incidence when compared to controls. The only statistically significant neoplasia seen in the study was an increase in male adrenal phaeochromocytomas at 80 ppm, but not at 250 ppm. The incidence of adrenal phaeochromocytoma bearing males (left or right adrenal was calculated from the individual animal data) in control, 2, 10, 80 or 250 ppm were, respectively, 5/70, 3/70, 2/70,

11*/70 and 7/70 for males that died or were sacrificed. [* Significant at $p < 0.019$ by a Peto analysis, when the 80 ppm group was compared with control]. None of these adrenal tumors were seen at the interim sacrifice.

This chronic/carcinogenicity study in the rat is ACCEPTABLE (GUIDELINE) and satisfies the guideline requirement for a chronic/carcinogenicity study OPPTS 870.4300); OECD 453] in the rat. This study was upgraded from supplementary (TXR#009746) to acceptable by a 3/12/1996 peer review committee (TXR# 011840). The confusion in TXR# 009746 over which enantiomer was studied is corrected from [R] in TXR# 009746 to [RS]. The test material studied was PP009, the [RS] racemic mixture. The conclusions take precedence over previous conclusions. This study was difficult to review. Parts of the report (MRID# 41563703) were unreadable making it necessary to refer to other pages for confirmation.

4.4.13.2 Carcinogenicity Study in Hamsters

In a carcinogenicity study (MRID# 45345401, 46082905) [fluazifop-P-butyl, 91.6% a.i., batch/lot# P23] was administered to 63 Golden Syrian hamsters/sex/dose in the diet at dose levels of 0, 0, 200, 750 or 3000 ppm (mean of measured test material consumption equivalent to 0, 0, 12.5, 47.4 or 193.6 mg/kg bw/day for males and 0, 0, 12.1, 45.5 or 181.4 mg/kgbw/day for females, page 25 of 45345401) for 80 weeks. Of these animals, 12/sex/group were designated for interim sacrifice on week 53. Two control groups were included.

There were no significant definitive body weight changes or meaningful food consumption or food efficiency differences from control in males or females during the study. There was an increased frequency of a clinical observation at 3000 ppm ("thin") (13 versus 5 in control). Survival was unchanged statistically, but females showed a slight nominal decrease at 3000 ppm (70.6% versus 78.5% in pooled control).

Probably no biologically significant hematological effects were seen in the study. Statistically significant decreases in white cell count in interim sacrificed males (22%-23%) at 750 ppm and 3000 ppm and in terminal females (17%) at 3000 ppm were observed. The remaining statistically significant hematological changes at 3000 ppm were minor and probably not biologically significant. No clinical chemistry analysis was conducted.

Testes weights were decreased at 750 and 3000 ppm and liver and kidney weights were increased in males and females at 3000 ppm. In males, absolute and adjusted testes weights were decreased in a dose related manner and statistically significantly reduced ($p < 0.01$) at 750 (abs 8% and adj 10%) and 3000 ppm (abs 20% and adj 19%). In males, adjusted liver weight was statistically significantly elevated at 750 (5%) and 3000 ppm (7%), but the absolute weight was not elevated at any dose level. In males and females, a kidney weight (males 11% and females 9%) and adjusted kidney weights (males 11% and females 9%) were statistically significantly elevated in the 3000 ppm group, only. In females absolute liver weight was statistically significantly elevated at all dose levels (9%-38%), but adjusted liver weights (34%) were significantly elevated only at 3000 ppm. Slight absolute and adjusted brain weight increases (2.5% and 1.6%) respectively in males and females at 3000 ppm are of unknown

biological significance.

Non-neoplastic microscopic histological findings were increased in the epididymis, testes, eyes, livers and gall bladder in males and in females, ovarian stroma cell/sex cord hyperplasia was increased at 750 and 3000 ppm. In males dose related incidences were seen at 750 ppm of reduced spermatozoa in epididymis (24% versus 8% in pooled controls), increased incidences of testicular tubule degeneration (37% versus 7% in pooled controls), increased incidences of eye cataract changes (31% in males at 750 ppm versus 16% in pooled controls), increased incidences of male liver mononuclear cell infiltration (35% versus 20% in pooled controls) and increased incidences of gall bladder stones (73% versus 31% in pooled controls) in males and in females at 3000 ppm (41% versus 13% in pooled controls). The incidence of chronic nephropathy was nominally increased in males and females at all dose levels. In females dose related increased incidences were seen at 750 ppm in ovarian stroma/sex cord hyperplasia (14%versus 6% in pooled controls).

The LOAEL for systemic effects is 750 ppm (equivalent to 47.4 mg/kg/day in males and 45.5 mg/kg/day in females) based on increased incidence of males with reduced sperm, testicular degeneration, eye cataract changes, liver inflamation and gall stones and in females increased incidences of ovarian stroma cell/sex cord hyperplasia. The NOAEL is 200 ppm (equivalent to 12.5 mg/kg/day in males and 12.1 mg/kg/day in females.

No dose related tumors were seen in males. Benign ovarian stroma cell/sex cord tumors were statistically significantly elevated at the 3000 ppm 5/51 (9.8%) versus 3/103 (2.9%) in pooled controls. However, when the incidence of malignant and benign tumors were combined, no significant differences were seen at any dose. It was concluded that fluazifop-butyl, [R] isomer is not carcinogenic at the dose levels studied. Dosing was adequate in males and females as indicated by the kidney weight increase and histological findings in eyes [cataracts], liver [inflammation], gall bladder [gall stones], the testes [tubular degeneration] and epididymis [reduced spermatozoa] of males, and in females by the ovarian findings [hyperplasia and adenomas], gall bladder [gall stones] and the severity of progressive chronic nephropathy at 3000 ppm (HDT).

The carcinogenicity study [MRID#46082901, but not 45345401] in the hamster is ACCEPTABLE (guideline) and does satisfy the guideline requirement for a carcinogenicity study [OPPTS 870.4200; OECD 451] in hamsters.

4.4. 13.3 Classification of Carcinogenic Potential

The Assessment team, in accordance with the 1999 Draft Carcinogen Risk Assessment Guideline (April, 1999) classified fluazifop-butyl and fluazifop-P-butyl as “Not likely to be carcinogenic in humans,” based on the lack of evidence of carcinogenicity in rats and hamsters.

Table 4.4 Summary of Toxicological Doses and Endpoints for Fluazifop-butyl & Fluazifop-P-butyl			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**Special FQPA SF* and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary (Females 13-49 years of age)	NOAEL = **50** mg/kg/day UF = 100 **Acute RfD** = **0.50** mg/kg	FQPA SF = **1X** **aPAD** = acute RfD / FQPA SF = 0.50 mg/kg	**Developmental Toxicity in rats** LOAEL = 200 mg/kg/day based on diaphragmatic hernia
Acute Dietary (General population including infants and children)	An appropriate endpoint attributable to a single dose was not identified in the available studies including the developmental toxicity studies.		
Chronic Dietary (All populations)	NOAEL= **0.74** mg/kg/day UF = 100 **Chronic RfD** = **0.0074** mg/kg/day	FQPA SF = **1X** **cPAD** = chronic RfD / FQPA SF = **0.0074** mg/kg/day	**Two-Generation Reproduction in rats** LOAEL = 5.8 mg/kg/day in males and 7.1 in females based on decreased spleen, testes & epididymal weights in males and uterine & pituitary weights in females
Short-Term Incidental Oral (1-30 days)	Maternal NOAEL = 100 mg/kg/day	**Residential** LOC for MOE = 100 **Occupational** = NA	**Developmental Toxicity Study in rats** LOAEL = 300 mg/kg/day based on maternal body weight gain decrement during GD 7-16.
Intermediate-Term Incidental Oral (1- 6 months)	Parental/ Systemic NOAEL= 0.74 mg/kg/day	**Residential** LOC for MOE = 100 **Occupational** = NA	**Two-Generation Reproduction in rats** LOAEL = 5.8 mg/kg/day in males and 7.1 in females based on decreased spleen, testes & epididymal weights in males and uterine & pituitary weights in females
Short-Term Dermal [a] (1 to 30 days) *	Developmental NOAEL= 2.0 mg/kg/day	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	**Developmental Toxicity Study in rats** LOAEL = 5.0 mg/kg/day based on fetal weight decrement, hydroureter and delayed ossification
Intermediate & Long-Term Dermal [a] (1 to >6 months)	Parental/ Systemic NOAEL= 0.74 mg/kg/day	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	**Two-Generation Reproduction in rats** LOAEL = 5.8 mg/kg/day in males and 7.1 in females based on decreased spleen, testes & epididymal weights in males and uterine & pituitary weights in females
Short-Term Inhalation [b] 1 to 30 days)*	Developmental NOAEL= 2.0 mg/kg/day	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	**Developmental Toxicity Study in rats** LOAEL = 5.0 mg/kg/day based on fetal weight decrement, hydroureter and delayed ossification

Table 4.4 Summary of Toxicological Doses and Endpoints for Fluazifop-butyl & Fluazifop-P-butyl			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**Special FQPA SF* and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Intermediate & Long-Term Inhalation [b] (1 to >6 months)	Parental/ Systemic NOAEL= 0.74 mg/kg/day	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	**Two-Generation Reproduction in rats** LOAEL = 5.8 mg/kg/day in males and 7.1 in females based on decreased spleen, testes & epididymal weights in males and uterine & pituitary weights in females
Cancer (oral, dermal, inhalation)	"Not likely to be carcinogenic to humans."		

* Selected by the Assessment team for Females 13-49 years of age. However, for risk assessment purposes this endpoint was used for all populations and is protective of effects seen at higher doses in other studies.

[a] Use either 9% (low exposure scenario) or 2% (high exposure scenario) for route-to-route extrapolations

[b] Absorption via the inhalation route is presumed to be equivalent to oral absorption.

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable

4.5 Endocrine disruption

EPA is required under the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

In the available studies on fluazifop–P-butyl, there was no estrogen, androgen and/or thyroid mediated toxicity shown. *In vitro* studies on human receptors included in yeast cells failed to detect any agonistic or antagonistic estrogen or androgen activity with fluazifop-butyl, fluazifop-P-butyl or fluazifop acid. Short term studies also failed to detect any meaningful gonadotropic hormone changes in rats. However, it is noted that testes and uterine weights were decreased in rats with only equivocal evidence of histological involvement. In addition, the study in hamsters showed decreased testes weights and ovarian sex cord hyperplasia. The testes and uterine weight decrement and ovarian sex cord hyperplasia suggest the possibility of endocrine mediated effects on these organs.

When additional appropriate screening and/or testing protocols being considered under

the Agency's EDSP have been developed, fluazifop-P-butyl may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

5.0 Public Health Data

No NHANES or AG HEALTH data are available for fluazifop-butyl or fluazifop-P-butyl.

5.1 Incident Reports

The following data bases have been consulted for the poisoning incident data on the active ingredient Fluazifop Butyl (PC Code: 122805 and 122809). See *Review of Fluazifop Butyl Incident Reports. DP Barcode D299665. Chemical#122805 and 122809. Jerome Blondell and Monica S. Hawkins. March 10, 2004*:

1) OPP Incident Data System (IDS) - reports of incidents from various sources, including registrants, other federal and state health and environmental agencies and individual consumers, submitted to OPP since 1992. Reports submitted to the Incident Data System represent anecdotal reports or allegations only, unless otherwise stated.

2) Poison Control Centers - as the result of a database purchased by EPA, OPP received Poison Control Center data covering the years 1993 through 1998 for all pesticides. Most of the national Poison Control Centers (PCCs) participate in a national data collection system, the Toxic Exposure Surveillance System which obtains data from about 65-70 centers at hospitals and universities.

3) California Department of Pesticide Regulation - California has collected uniform data on suspected pesticide poisonings since 1982. Physicians are required, by statute, to report to their local health officer all occurrences of illness suspected of being related to exposure to pesticides. The majority of the incidents involve workers. Information on exposure (worker activity), type of illness (systemic, eye, skin, eye/skin and respiratory), likelihood of a causal relationship, and number of days off work and in the hospital are provided.

4) National Pesticide Telecommunications Network (NPTN) - NPTN is a toll-free information service supported by OPP. A ranking of the top 200 active ingredients for which telephone calls were received during calendar years 1984-1991, inclusive has been prepared. The total number of calls was tabulated for the categories human incidents, animal incidents, calls for information, and others.

Relatively few incidents of illness have been reported due to fluazifop butyl or fluazifop-P-butyl. The overwhelming majority of cases occurred among handlers who experienced skin or eye effects. Skin and eye protection is recommended for handlers of this pesticide.

5.2 Other

No scientific literature pertinent to additional health effects of fluazifop butyl or fluazifop-P-butyl in humans was located.

6.0 Exposure Characterization/Assessment

6.1 Dietary Exposure/Risk Pathway

6.1.1 Residue Profile

Tolerances are established under 40 CFR §180.411(a)(1) and (c)(1) for residues of fluazifop-butyl and free and conjugated fluazifop, expressed as fluazifop, in/on cotton commodities, soybean commodities, tabasco pepper, and animal commodities, and under §180.411(a)(2) and (c)(2) for residues of fluazifop-P-butyl and free and conjugated fluazifop ® isomer), expressed as fluazifop, in/on asparagus, carrots, coffee, endive, macadamia nuts, onion, pecans, rhubarb, spinach, stone fruit, and sweet potatoes. See Tolerance Reassessment Table and details in the revised Residue Chemistry chapter (12/08/04). The tolerances are adequate at existing levels pending completion of the review of the submitted data.

For enforcement of tolerances for fluazifop-P-butyl residues of concern, an HPLC/UV method is available for crop commodities, and HPLC/UV and GC/MS methods are available for animal commodities. The stated quantitation limits are 0.02-0.05 ppm for crop commodities, 0.01 ppm for milk, and 0.02 ppm for animal tissues.

The Phase 4 Reviews for fluazifop-butyl and fluazifop-P-butyl were completed 2/26/91. The Phase 4 Reviews identified many studies that were adequate for Phase 5 review; however, Phase 5 review of these studies has not yet been completed. The information contained in this document outlines the Residue Chemistry Science Assessments with respect to the Report on FQPA Tolerance Reassessment Progress and Interim Risk Management Decisions (TRED) for fluazifop-P-butyl.

6.1.2 Acute and Chronic Dietary Exposure and Risk

Fluazifop-P-butyl acute and chronic dietary exposure assessments were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 2.03), which incorporates consumption data from USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996 and 1998. The 1994-96, 98 data are based on the reported consumption of more than 20,000 individuals over two non-consecutive survey days. Foods "as consumed" (e.g., apple pie) are linked to EPA-defined food commodities (e.g. apples, peeled fruit - cooked; fresh or N/S; baked; or wheat flour - cooked; fresh or N/S, baked) using publicly available recipe translation files developed jointly by USDA/ARS and EPA. For chronic exposure assessment, consumption data are averaged for the entire U.S. population and within population subgroups, but for acute exposure assessment are retained as individual consumption events. See *Fluazifop-p-butyl. Revised Acute and Chronic Dietary Exposure Assessments for the Tolerance Reassessment Eligibility Decision (TRED). PC Code:122809. DP Barcode: D310695. Sherrie L. Kinard. December 8, 2004.*

Acute Dietary Exposure Results and Characterization: An acute dietary exposure analysis (food + water) was performed in order to estimate the acute exposure and risks which result from the registered uses of fluazifop-P-butyl. Tolerance level with a ratio adjustment for additional metabolites of concern, 100% CT, and default processing factors were used in these assessments. A screening-level estimate was used to assess the dietary exposure and risks from

residues in water. No refinements were included for the acute dietary exposure analysis; therefore this is considered to be a conservative assessment. Dietary risk estimates are provided for the population subgroup of females 13-49 years of age. This assessment concludes that for all supported registered commodities, the acute dietary risk estimates are < 2% aPAD, which are below the Agency's level of concern (< 100 % aPAD) at the 95th exposure percentile.

Chronic Dietary Exposure Results and Characterization: Chronic dietary exposure analyses were also performed in order to estimate the chronic exposure and risks which result from the registered uses of fluazifop-P-butyl. Tolerance level with a ratio adjustment for additional metabolites of concern, %CT estimates, and default processing factors were used in these assessments. A screening-level estimate was used to assess the dietary exposure and risks from residues in water. No additional refinements were included. Dietary risk estimates are provided for the U.S. population (total) and various population subgroups. This assessment also concludes that for all commodities, the chronic dietary risk estimates are below the Agency's level of concern (<100 %cPAD) for the U.S. population (30% cPAD) and all population subgroups. The most highly exposed population subgroup in the chronic dietary exposure analysis is all infants less than 1 year of age (95% cPAD). The most significant contributions (dietary "drivers") to the risk are water, carrot babyfood, and spinach babyfood. This assessment is still considered to be conservative since tolerance and screening level estimates were used.

Cancer Dietary Exposure Results and Characterization: Fluazifop-P-butyl is classified as a "not likely to be carcinogenic to humans"; therefore, no dietary assessment has been performed at this time.

Table 6.1 Summary of Dietary Exposure and Risk for Fluazifop-P-butyl

Population Subgroup*	Acute Dietary (95th Percentile)		Chronic Dietary		Cancer	
	Dietary Exposure (mg/kg/day)	% aPAD*	Dietary Exposure (mg/kg/day)	% cPAD*	Dietary Exposure (mg/kg/day)	Risk
General U.S. Population	NA	NA	0.002244	30.3	N/A	N/A
All Infants (< 1 year old)			**0.007010**	**94.7**		
Children 1-2 years old			0.005130	69.3		
Children 3-5 years old			0.003915	52.9		
Children 6-12 years old			0.002531	34.2		
Youth 13-19 years old			0.001589	21.5		
Adults 20-49 years old			0.001917	25.9		
Adults 50+ years old			0.002025	27.4		
Females 13-49 years old	0.008193	1.6	0.001918	25.9		

** Report %PADs to 2 significant figures.*
Note. The values for the highest exposed population for each type of risk assessment should be bolded.

6.2 Water Exposure/Risk Pathway

Limited monitoring data are available for fluazifop-P-butyl therefore, drinking water expected concentrations (DWEC) were calculated from models for risk assessment purposes. Fluazifop-P-butyl is rapidly (less than one day) degraded in soil to fluazifop acid, which is much more stable in soil and water environments than the parent. At present, all tolerances for fluazifop-P-butyl are expressed as the acid. Other degradates are formed in only minor amounts. Therefore, EFED modeled the combined residue of fluazifop-P-butyl plus fluazifop acid for the drinking water assessment. Because fluazifop acid is the form present for the great majority of the time, its physical properties were used in the modeling.

Ground Water - EFED used the Tier 1 SCIGROW model and a total application rate of 1.125 lb a.i. per acre per year (maximum rate), a mean soil half-life of 18 days, and a Koc of 8.3 mL/g for fluazifop acid, to predict a concentration of 0.58 ppb in ground water. See *Tier 1 Drinking Water Assessment for Fluazifop-p-butyl. William P. Eckel. October 29, 2004.*

The SCIGROW model predicts the impact on ground water from a single season's use of a chemical. The properties of fluazifop acid, namely high mobility and long persistence in water (78-day hydrolysis half-life at pH 7) and anaerobic soil (half-life 1 to 3 years, MRID# 92067033) indicate that it might persist from year to year in the subsurface, and move with flowing ground water. Thus, the screening value of 0.58 ppb may not adequately describe the expected behavior of fluazifop acid. At this time, EFED is unable to further refine ground water estimates. The screening value of 0.58 ppb was used for both acute and chronic exposure estimates.

Surface Water - In the Tier 1 drinking water assessment, the highest chronic DWEC was 12 ppb for the tree fruit use. The asparagus uses had chronic DWECs of 11 and 10 ppb (the latter being for a 24(c) label.) The Tier 1 drinking water assessment noted that the DWECs for tree fruits and asparagus were higher than those for the major uses (soybeans and cotton) because EFED used the default percent cropped area (PCA) factor of 87%, the highest labeled use rates, as well as the maximum number of applications, and minimum application intervals. Thus, the Tier 1 DWECs are high-end estimates of expected concentrations in raw (untreated) drinking water.

For a more refined Tier 2 analysis, EFED chose to model two tree fruit scenarios; California fruit (plums) and Georgia peaches. These scenarios were chosen because tree fruit has the highest labeled use rates (1.125 lb a.i./A/yr), and gave the highest DWECs in the Tier 1 analysis. Fluazifop-P-butyl is used to kill grasses in orchards, and is used as a ground spray directed at the grass. Currently, EFED does not have PRZM scenarios for asparagus. The Tier 2 model is PRZM-EXAMS with the Index Reservoir scenario. See *Tier 2 Drinking Water Assessment for Fluazifop-P-butyl and its Major Degradate Fluazifop-acid. William P. Eckel. June 30, 2004*.

Table 6.2. Summary of Estimated Surface and Ground Water Concentrations for the Combined Residues of Fluazifop-P-butyl and Fluazifop Acid.

Exposure Duration	Fluazifop-P-butyl	
	Surface Water Conc., ppb [a]	Ground Water Conc., ppb [b]
Acute	8.7	0.58

Table 6.2. Summary of Estimated Surface and Ground Water Concentrations for the Combined Residues of Fluazifop-P-butyl and Fluazifop Acid.		
Exposure Duration	**Fluazifop-P-butyl**	
	Surface Water Conc., ppb [a]	**Ground Water Conc., ppb [b]**
Chronic (non-cancer)	3.1	0.58
Chronic (cancer) [c]	1.4	0.58

[a] From the Tier II PRZM-EXAMS - Index Reservoir model. Input parameters are based on default PCA 0.87 & a total application rate of 1.125 lb. a.i./A/yr incorporating 3 applications at 21 day intervals for GA peaches.
[b] From the SCI-GROW model assuming a seasonal use rate of 1.125 lb ai/A/yr, a K_{oc} of 8.3 mL/g, and a mean soil half-life of 18 days.
[c] Though an estimate for cancer assessment (average of 30 chronic DWECs) was provided, no cancer risk assessment is needed.

Monitoring Data - The registrant reported that a search of U.S. Geological Survey data bases yielded no monitoring data on fluazifop-P-butyl. The Agency for Toxic Substances and Disease Registry (ATSDR) found fluazifop in the community drinking water wells of McFarland, Kern County, California, an agricultural community, in 1995. Concentrations of 0.06, 0.16, and 0.17 ppb were found, which are about the same order of magnitude as the SCI-GROW screening concentration.

6.3 Residential (Non-Occupational) Exposure/Risk Pathway

At this time, products containing fluazifop-P-butyl are intended for both occupational and non-occupational uses. Fluazifop-P-butyl is a selective herbicide used in the post-emergent control of grasses in agricultural, ornamental, residential and recreational (golf courses) settings. Fluazifop-P-butyl has several occupational uses that will not be addressed in this TRED. The fluazifop-P-butyl end-use products are formulated as liquid concentrates and ready-to-use liquids. See *Fluazifop-p-butyl: REVISED Residential Exposure Assessment and Recommendations for the Tolerance Reassessment Eligibility Decision (TRED) Document. Margarita Collantes. November 29, 2004.*

In residential settings, fluazifop-P-butyl is used on residential turfgrass, on broadleaf ornamentals, and for total grass weed control for lawn renovations, and around driveways, fence lines, sidewalks, and similar areas. The current maximum application rate for homeowner and lawn care operator (LCO) application to residential turfgrass and golf courses is 0.09 pounds active ingredient per acre for selective weed control (Ornamec by PBI Gordon Corp, EPA Reg. No. 2217-728). The current maximum application rate for lawn renovation is 0.98 pounds active ingredient per acre for homeowners (Grass and Weed Killer by Chemsico, EPA Reg. No. 9688-106) and 0.73 pounds active ingredient for LCOs. The maximum application rate for application to residential ornamentals is 0.44 pounds active ingredient per acre (0.01 pounds active ingredient per 1000 square feet). In addition, on November 26, 2003, the technical registrant for fluazifop-P-butyl, Syngenta, submitted a use closure memo indicating the following application rates being supported for the technical reregistration: 0.075 lb ai/A for turf and 0.375 lb ai/A for non crops and ornamentals.

Table 6.3. Summary of Maximum Application Rates for Fluazifop-P-butyl Uses in Residential Settings

Target	Application Rate	Application Equipment	Area Treated Daily
Commercial Uses at Residential Sites			
Lawn renovation	0.005 lb ai/gal & 0.73 lb ai/A	Low pressure handwand	Not applicable to this assessment
		Backpack sprayer	
		Handgun	
Non-crop areas (including cemeteries, around buildings, parkways, roadsides, landscaped areas	0.38 lb ai/A	Low pressure handwand	
		Backpack sprayer	
		Handgun	
Turf (suppression/ control of weeds in Zoysia and Tall Fescue), including golf courses, around residential, commercial, public, and industrial buildings and areas, sports fields, parks [One label does not prohibit applications to home lawns.]	0.09 lb ai/A (Reg .# 2217-728) 0.075 lb ai/A (Reg. #100-1069)	Low pressure handwand	
		Backpack sprayer	
		Handgun	
Ornamentals, trees, shrubs, and groundcovers	0.01 lb ai/gal or 0.44 lb ai/A	Low pressure handwand	
		Handgun	
		Watering Can	
Residential (Homeowner) Uses			
Walks, drives, patios and fences, and lawn renovation	0.0056 lb ai/gallon or 0.98 lb ai/A (Reg. #9688-106) 0.075 lb ai/A (Reg.# 100-1069)	Low pressure handwand	5 gallons
		Hose-end sprayer	0.5 acre
		Watering can	5 gallons
In and around ornamentals and groundcover	0.0056 lb ai/gallon	Watering can	5 gallons
	0.04 lb ai/ gallon (ready-to-use)	Sprinkling Application	1 gallon
		Trigger-pump sprayer	1 gallon

Short-term exposures (defined as exposures from 1 to 30 days in duration) may occur for residents applying fluazifop-P-butyl products and for residents exposed to fluazifop-P-butyl following applications in residential settings. Intermediate- and long-term exposures are not anticipated for residential handling or postapplication exposures. The Assessment team selected two separate short-term dermal and inhalation endpoints of concern for fluazifop-P-butyl – one for females of childbearing age (2 mg/kg/day) and another for the general population, including

infants and children (100 mg/kg/day). Since mitigating risks for one subpopulation and not for another is not considered feasible at this time, HED assessed short-term dermal and inhalation risks using the NOAEL of 2 mg/kg/day. The short-term dermal (noncancer) endpoint for fluazifop-P-butyl is from an oral study, therefore, a dermal absorption factor must be used. The assessment team determined that a dermal absorption factor of 9% should be used to assess risks from low exposures and a dermal absorption factor of 2% should be used to assess risks from high exposures. For the purposes of this residential risk assessment, HED assumes that:

• the 9% dermal absorption factor is appropriate for assessing dermal exposure to residential handlers and for assessing postapplication dermal exposures during golfing or mowing residential lawns – all of which are considered representative of low exposure activities, and

• the 2% dermal absorption factor is appropriate for assessing high contact dermal exposure on residential lawns – which are considered more representative of high exposure activities.

6.3.1 Home Uses

Residential handlers are involved in the entire pesticide application process (i.e., they do all functions related to a pesticide application event). The only significant difference between this category and the similar occupational category is that the individuals typically use less chemical on a daily basis and residents are assumed to wear attire consisting of short-sleeve shirt, short pants, shoes, and socks.

The fluazifop-P-butyl assessment reflects the Agency's current approaches for completing residential exposure assessments based on the guidance provided in the OPPTS Harmonized Guidelines, Series 875: Occupational and Residential Exposure Test Guidelines, Group B: Postapplication Exposure Monitoring Test Guidelines, the Draft: Standard Operating Procedures (SOPs) for Residential Exposure Assessment, and the Overview of Issues Related to the Standard Operating Procedures for Residential Exposure Assessment presented at the September 1999 meeting of the FIFRA Scientific Advisory Panel (SAP). The Agency is, however, currently in the process of revising its guidance for completing these types of assessments.

6.3.1.1 Residential Handlers

Scenarios used to define risks are based on the *U.S. EPA Guidelines For Exposure Assessment* (U.S. EPA; Federal Register Volume 57, Number 104; May 29, 1992). Assessing exposures and risks resulting from residential uses is very similar to assessing occupational exposures and risks, with the following exceptions: 1) residential handler exposure scenarios are considered to be short-term only, due to the infrequent use patterns associated with homeowner products, 2) homeowner handler assessments are based on the assumption that individuals are wearing shorts, short-sleeved shirts, socks, and shoes [no personal protective equipment (PPE)], and 3) homeowner handlers are expected to complete all tasks associated with the use of a pesticide product including mixing/ loading, if needed, as well as the application.

It has been determined that exposure to pesticide handlers is likely during the residential use of fluazifop-P-butyl in a variety of outdoor environments, including on lawns, walks, drives and ornamentals. The anticipated use patterns and current labeling indicate several residential

handler exposure scenarios based on the types of equipment and techniques that can potentially be used to make fluazifop-P-butyl applications. The quantitative exposure/risk assessment developed for residential handlers is based on these scenarios.

Mixer/Loader/Applicators:

(1) Liquid Concentrate: Low Pressure Handwand (ORETF data)
(2) Liquid Concentrate: Hose-end Sprayer (ORETF data)
(3) Liquid Concentrate: Watering Can (ORETF hose-end sprayer data)
(4) RTU Formulations: Sprinkling Application (ORETF hose-end sprayer data)
(5) RTU Formulations: Trigger-pump Sprayer (proprietary data)

Note: the ready-to-use (RTU) formulation has two options for application – use as a trigger-pump sprayer and use by sprinkling the liquid directly from the container. Therefore, two different exposure scenarios are assessed.

A series of assumptions and exposure factors served as the basis for completing the residential handler risk assessments. Each assumption and factor is detailed below. In addition to these factors, unit exposure values were used to calculate risk estimates. Mostly, the unit exposure values were taken from the ORETF studies, however, one proprietary study (MRID# 447393-01) was used. Since ORETF does not include data for scenarios using ready-to-use spray bottle application, data from a proprietary study were used to estimate those exposures (MRID# 447393-01).

The risk calculations for residential fluazifop-P-butyl handlers completed in this assessment are included in Table 6.3.1.1. The results indicate that all of the residential handler risks are not of concern [i.e., MOEs are all greater than LOC of 100]. In order to refine this residential risk assessment, more data on actual use patterns including rates, timing, and areas treated would better characterize fluazifop-P-butyl risks.

Table 6.3.1.1: Summary of Residential Handler Risks from Fluazifop-P-butyl										
Exposure Scenario	Target	Application Rate[a]	Area Treated Daily[b]	Dermal Unit Exposure (mg/lb ai)	Inhalation Unit Exposure (µg/lb ai)	Dermal Dose (mg/kg/day)	Inhalation Dose (mg/kg/day)	MOE (HED's level of concern = 100)		
								Dermal[d]	Inhalation[e]	Dermal + Inhalation
Mixer/Loader/Applicator										
Mixing/Loading/Applying Liquid Concentrates with Low Pressure Handwand (ORETF residential handheld pump sprayer data) (1)	Walks, drives, patios, and fences	0.0056 lb ai/gallon	5 gallons	56	3.8	0.0024	0.0000018	850	1,100,000	850
Mixing/Loading/Applying Liquid Concentrates with Hose-End Sprayer (Residential ORETF data) (2)	Walks, drives, patios, and fences, lawn replacement	0.98 lb ai/acre	0.5 acre	11	17	0.0081	0.00014	250	14,000	240
Mixing/Loading/Applying Liquid Concentrates with a Watering Can (using ORETF residential hose-end data) (3)	Walks, drives, patios, and fences	0.0056 lb ai/gallon	5 gallons	11	17	0.00046	0.0000079	4300	250,000	4300
Loading/Applying Ready-To-Use Liquid with a Watering Can (using ORETF residential hose-end data) (4)	in around ornamentals and ground cover	0.04 lb ai/gallon	1 gallons	11	17	0.00066	0.000011	3000	180,000	3000
Applying Ready to Use Liquid via Trigger-Pump Sprayer (using proprietary data) (5)	in around ornamentals and ground cover	0.04 lb ai/gallon	1 gallons	13.5	123	0.00081	0.000082	2500	24,000	2200

Footnotes

a Application rates are the maximum application rates determined from EPA registered labels for fluazifop-P-butyl.

b Amount handled per day values are EPA estimates.

c Attire is short-sleeve shirt, short pants, and no gloves and no respirator.

d Dermal MOE = NOAEL (2 mg/kg/day) / dermal daily dose (mg/kg/day), where dermal dose = daily unit exposure (mg/lb ai) x application rate x amount handled per day / body weight (60 kg female adult).

e Inhalation MOE = NOAEL (2 mg/kg/day) / inhalation daily dose (mg/kg/day), where inhalation dose = daily unit exposure (µg/lb ai) x application rate x amount handled per day x conversion factor (1mg/1,000 µg) / body weight (60 kg adult female).

6.3.1.2 Residential/Recreational Postapplication Exposures and Risks

HED uses the term "postapplication" to describe exposures to individuals that occur as a result of being in an environment that has been previously treated with a pesticide. Fluazifop-P-butyl can be used in many areas that can be frequented by the general population including residential areas (e.g., home lawns). As a result, individuals of varying ages can be exposed by entering these areas if they have been previously treated and different age groups should be considered in different situations. The populations that were considered in the assessment include:

• **Residential Adults:** these individuals are members of the general population that are exposed to chemicals by engaging in activities at their residences (e.g., in their lawns) and also in areas not limited to their residence (e.g., golf courses or parks) previously treated with a pesticide. These kinds of exposures are attributable to a variety of activities and are usually addressed by HED in risk assessments by considering a representative activity as the basis for the exposure calculation.

• **Residential Children:** children are members of the general population that can also be exposed in their residences (e.g., on lawns and other residential turfgrass areas). These kinds of exposures are attributable to a variety of activities such as playing outside. Toddlers have been selected as the sentinel (representative) population for turf. Youth-aged children (ages 10 to 12) are considered the sentinel population for a golfing assessment, because it is likely that children of this age would play golf. Children are addressed by HED in risk assessments by considering representative activities for each age group in an exposure calculation.

The *SOPs For Residential Exposure Assessment* define several scenarios that apply to uses specified in current fluazifop-P-butyl labels. These scenarios served as the basis for the residential postapplication assessment along with the modifications to them and the additional data and approaches described above. HED used this guidance to define the exposure scenarios that essentially include dermal and nondietary ingestion (hand-to-mouth, object-to-mouth, ingestion) exposure to toddlers on treated lawns, dermal exposure to youths on treated golf courses, and dermal exposure to adults on treated lawns and on treated golf courses. The SOPs and the associated scenarios are presented below:

The assumptions and factors used in the risk calculations are consistent with current Agency policy for completing residential exposure assessments (i.e., *SOPs For Residential Exposure Assessment*) and can be found in detail in section 3.2.2 of *Fluazifop-p-butyl: REVISED Residential Exposure Assessment and Recommendations for the Tolerance Reassessment Eligibility Decision (TRED) Document. Margarita Collantes. November 29, 2004*. The body weight of an average adult female (60 kilograms) was used for assessing dermal risks to adults, since the toxicological endpoint of concern is female-specific. Also, HED combines risks resulting from exposures to individual applications when it is likely they can occur simultaneously based on the use pattern and the behavior associated with the exposed population. For fluazifop-p-butyl, HED has combined risks (i.e., MOEs) for turf scenarios involving toddlers – dermal plus hand-to-mouth plus object-to-mouth plus soil ingestion.

Two separate dermal absorption values are used – 9% is used for assessing dermal exposures while golfing or while mowing a lawn, since these are representative of low exposure

activities, whereas 2% is used for assessing dermal exposures from high contact lawn activities, since these are representative of high exposure activities.

Noncancer risks were calculated using the MOE approach, which is a ratio of the body burden to the toxicological endpoint of concern. Exposures were calculated by considering the potential sources of exposure (i.e., TTRs on lawns), then calculating dermal and non-dietary ingestion exposures.

To estimate turf transferrable residue (TTR) values and dislodgeable foliar residue (DFR) values when no chemical-specific TTR or DFR data are available, HED assumes that a certain percent of the turf application rate is available for transfer on day 0. Then HED converts the application rate (in pounds active ingredient per acre) to micrograms per square centimeter using conversion factors. Five percent of the application rate has been used to calculate the day 0 TTR residue levels used for assessing risks from dermal and hand-to-mouth exposures, and 20 percent of the application rate has been used to calculate the day 0 residue levels used for assessing risks from object-to-mouth behaviors.

Adults

Table 6.3.1.2a presents the fluazifop-p-butyl postapplication MOE values calculated for adults after applications to golf courses, to established lawns and to lawns slated for renovation. All MOEs are >100 on the day of application.

Table 6.3.1.2a. Adult Residential Risk Estimates for Postapplication Exposure

Exposure Scenario	Route of Exposure	Application Rate (lb ai/acre)	MOE at Day 0 (HED's level of concern = 100)
High Contact Lawn Activities	Dermal	0.98 (lawn renovation)	380
		0.09 (established turf)	4,100
		0.075 (turf)	5,000
Mowing Turf	Dermal	0.09 (established turf)	26,000
Golf Course	Dermal	0.09 (established turf)	13,000
		0.075 (turf)	16,000

Youth-aged children (10 to 12 years old)

Table 6.3.1.2b summarizes the postapplication MOE values calculated for youth following golf course applications of fluazifop-P-butyl. MOEs for youths were >100.

Table 6.3.1.2b: Youth Residential Risk Estimates for Postapplication Exposure			
Exposure Scenario	Route of Exposure	Application Rate (lb ai/acre)	MOE at Day 0 (HED's level of concern = 100)
Golf course	Dermal	0.09 (established turf)	8,600
		0.075	10,000

Toddler (3 year old)

Risks (MOEs) to toddlers were calculated for postapplication risks following the application of fluazifop-p-butyl to established home lawns and to lawns slated for renovation. Table 6.3.1.2c summarizes the risk assessment for toddlers. All MOEs are greater than HED's LOC of 100 on day 0.

Table 6.3.1.2c. Toddler Residential Postapplication Risk Estimates for Fluazifop-p-butyl			
Exposure Scenario	Route of Exposure	Application Rate (lb ai/acre)	MOE on Day 0 (HED's level of concern = 100)
Residential Turf (High Contact Activities)	Dermal	0.98 (lawn renovation)	260
		0.09 (established turf)	2,900
		0.075 (turf)	170,000
Hand to Mouth Activity on Turf	Oral	0.98 (lawn renovation)	6,800
		0.09 (established turf)	74,000
		0.075 (turf)	6,000,000
Object to Mouth Activity on Turf	Oral	0.98 (lawn renovation)	27,000
		0.09 (established turf)	300,000
		0.075 (turf)	360,000
Incidental Soil Ingestion	Oral	0.98 (lawn renovation)	2,000,000
		0.09 (established turf)	22,000,000
		0.075 (turf)	26,000,000

Combined Risk Assessment for Toddlers

HED combines risk values resulting from separate postapplication exposure scenarios when it is likely they can occur simultaneously based on the use-pattern and the behavior associated with the exposed population. Table 6.3.1.2d presents a summary of the combined risk assessments for exposures to toddlers following home lawn applications. The results of the combined postapplication risk assessment for toddlers indicates that the combined risks to toddlers on day 0 following applications to established lawns and to lawns slated for renovation are all greater than HED's LOC of 100.

Table 6.3.1.2d: Residential Scenarios for Combined Toddler Risk Estimates			
Postapplication Exposure Scenario		Margins of Exposure (MOEs) (HED's level of concern = 100)	
		Short-Term MOE	Combined Non-Dietary Risk
Lawn Renovation (0.98 lb ai/A)			
Toddler Risks following spray applications to lawns	Hand to Mouth	6,800	250
	Object to Mouth	27,000	
	Incidental Soil Ingestion	2,000,000	
	High Contact Dermal	260	
Established Lawns (0.09 lb ai/A)			
Toddler Risks following spray applications to lawns	Hand to Mouth	74,000	2,800
	Object to Mouth	300,000	
	Incidental Soil Ingestion	22,000,000	
	High Contact Dermal	2,900	
Turf (0.075 lb ai/A)			
Toddler Risks following spray applications to lawns	Hand to Mouth	6,000,000	110,000
	Object to Mouth	360,000	
	Incidental Soil Ingestion	26,000,000	
	High Contact Dermal	170,000	

HED considered a number of exposure scenarios for products that can be used in the residential environment representing different segments of the population including toddlers, youth-aged children, and adults. Short-term MOEs were calculated for all scenarios. In residential settings, HED does not use restricted-entry intervals or other mitigation approaches to limit postapplication exposures, because they are viewed as impractical and not enforceable. As such, risk estimates on the day of application would be the key concern. In this assessment however, HED has no postapplication risk concerns following the use of fluazifop-P-butyl in residential settings.

6.3.2 Other (Spray Drift, etc.)

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 fluazifop-P-butyl. Fluazifop-P-butyl labels indicate that it is registered for use on several major agricultural crops, including cotton, soybeans, fruit/nut trees, and vegetable crops. As such, it may be

applied with aircraft, groundboom, or airblast equipment. As indicated in this assessment, fluazifop-P-butyl is applied directly to residential turf and does not result in exposures of concern. Based on this assessment, HED believes that it is unlikely that there is a higher potential for risk from exposure to spray drift from agricultural uses of this chemical.

7.0 Aggregate Risk Assessments and Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures (oral, dermal, and inhalation exposures). 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.

In general, exposures from various sources (routes) are aggregated only when the toxic effects, determined by the endpoint selected for that route, are the same. In this case, a screening level aggregate assessment was performed using high-end exposures and conservative (lowest) endpoints. Further refinements would have been incorporated into the assessment if it had showed risks of concern.

7.1 Acute Aggregate Risk

The acute aggregate risk estimate includes the contribution of risk from dietary (food + drinking water) sources only. Acute risk estimates from exposures to food and water, associated with the use of fluazifop-P-butyl do not exceed the Agency's level of concern. The estimated acute dietary risk is < 2 % of the aPAD at the 95th percentile for females 13-49 years of age. No acute dietary endpoint was selected for the U.S. population and therefore, no dietary risk assessment was conducted (see Section 4.4).

Though some chemical-specific water monitoring data are available, they are extremely limited, not nationally representative and not at-the-tap data. Hence, they are unsuitable to be quantitatively included in an aggregate risk assessment. Therefore, drinking water expected concentrations (DWECs) were calculated from models, for risk assessment purposes, based on maximum application rates. EFED modeled the combined residue of fluazifop-P-butyl plus fluazifop acid for the drinking water assessment. The deterministic DWECs were combined directly with the acute dietary exposure assessment for females 13-49 years of age to calculate aggregate dietary (food + water) risk. The advantage of this approach, for females or any population subgroup, is that the actual individual body weight and water consumption data from the CSFII are used, rather than assumed weights and consumption for broad age groups. Surface water DWECs were combined with estimated food exposure for aggregate risk assessment purposes since the calculated surface water estimates exceed the calculated ground water estimates and therefore, are more conservative.

7.2 Short-Term Aggregate Risk

Aggregate short-term risk estimates include the contribution of risk from chronic dietary sources (food + water) and short-term residential sources. There are a number of exposure

scenarios that could be aggregated. For purposes of this assessment, the most likely exposure scenarios that might occur during the same time-frame were combined to provide a conservative (high-end) estimate of aggregate risk. As discussed in the Dose Selection section, the most conservative dose/endpoints were used for the dermal and inhalation routes.

Adult Aggregate Risk: Chronic food and water exposures for the U.S. general population and for females 13-49 years of age were combined with residential handler and postapplication exposures. Residential handler exposures for mixing/loading/applying liquid concentrates with a hose-end sprayer at 0.98 lb ai/A (max rate), dermal and inhalation, were combined, by route, with postapplication exposures (dermal) for lawn renovation, considered a high contact lawn activity, performed at 0.98 lb ai/A. To calculate the route-specific MOEs the dose/endpoints used were; oral 100 mg/kg/day; dermal 2 mg/kg/day; and inhalation 2 mg/kg/day.

Child/Toddler Aggregate Risk: Chronic food and water exposures for infants < 1 year of age were combined with postapplication residential hand to mouth plus object to mouth plus incidental soil ingestion exposures resulting from applications of fluazifop-P-butyl to lawns at 0.98 lbs ai/A. To calculate the route-specific MOEs the dose/endpoints used were; oral 100 mg/kg/day; and dermal 2 mg/kg/day.

Taking into account the supported uses proposed in this action, HED **can conclude with reasonable certainty** that combined residues of fluazifop-P-butyl from food, drinking water, and residential exposures would not likely result in a short-term aggregate risk of concern to any population subgroup. The short-term aggregate risks (MOEs) are greater than HED's LOC and therefore, not of concern, for all populations.

Table 7.2 Short-Term Aggregate Risk

Population	Short-Term Scenario					
	HED's Aggregate LOC[1]	**MOE food + water [2]**	**MOE incid oral[3]**	**MOE dermal[4]**	**MOE inhalation[5]**	**Aggregate MOE (food and residential)[6]**
U.S. Pop.	100	45,000	NA	150	14,000	150
Adult Female	100	52,000	NA	150	14,000	150
Child	100	14,000	5,500	260	NA	240

[1] *Level of Concern (LOC) is 100 based on 10X for inter-species extrapolation and 10X for intra-species variation.*
[2] MOE food + water = [(short-term oral NOAEL 100 mg/kg/day)/(chronic dietary exposure)]
Chronic dietary exposure: U.S. Pop.=0.0022 mg/kg/day; Females 13-49 yrs = 0.0019 mg/kg/day; Infants < 1 yr = 0.0070 mg/kg/d
[3] MOE incidental oral = [(short-term incidental oral NOAEL 100 mg/kg/day)/(child residential exposure)]
Child residential exposure: Hand-to-mouth = 0.015 mg/kg/day; Object-to-mouth = 0.0037 mg/kg/day; Incidental soil ingestion = 0.000049 mg/kg/day
[4] MOE dermal = [(short-term dermal NOAEL 2 mg/kg/day)/(high-end dermal residential exposure)]
Dermal exposure: Adults = handler 0.0081 mg/kg/day + postapp 0.0053 mg/kg/day; Child = 0.0076 mg/kg/day
[5] MOE inhalation = [(inhalation NOAEL 2 mg/kg/day)/(high-end inhalation residential exposure)]
Inhalation exposure: Adult = handler 0.00014 mg/kg/day
[6] Aggregate MOE (food + water + residential) = 1÷[[(1÷MOE food+water) + (1÷MOE incidental oral) + (1÷MOE dermal) + (1÷MOE inhalation)]]

7.3 Intermediate-Term Aggregate Risk

All residential/recreational exposures are expected to be short-term in duration.

7.4 Long-term Aggregate Risk

Aggregate long-term (noncancer) risk estimates include the contribution of risk from chronic dietary sources (food + water) and residential sources. However, based on the labeled uses, no long-term or chronic residential exposures are expected. Chronic risk estimates from exposures to food and water, associated with the use of fluazifop-P-butyl do not exceed HED's level of concern for the most highly exposed population subgroup, infants < 1 year of age. The chronic dietary risk estimate for infants was 95% of the cPAD.

As in the acute aggregate assessment, surface water DWECs were calculated by EFED to estimate the potential contribution to the chronic exposure from drinking water, and the DWECs were combined with chronic food exposures to estimate potential long-term aggregate risks from the uses of fluazifop-P-butyl.

7.5 Aggregate Cancer Risk

Fluazifop-P-butyl was classified as "not likely to be carcinogenic to humans."

8.0 Cumulative Risk Characterization/Assessment

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 fluazifop-P-butyl and any other substances and fluazifop-P-butyl does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that fluazifop-P-butyl 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 Office of Pesticide Programs 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/pesticides/cumulative/.

9.0 Occupational Exposure/Risk Pathway

This assessment supports the Tolerance Reassessment Eligibility Decision (TRED) document for fluazifop-p-butyl and addresses risks resulting from dietary and non-occupational (residential/recreational) exposures only. Occupational exposures/risks will not be addressed in this assessment.

10.0 Data Needs and Label Requirements

10.1 Residue Chemistry

1. The registrant must submit translated copies of labels for all foreign uses of fluazifop-P-butyl on coffee destined for import into the U.S. In addition, the following label amendments are required:

- All product labels which contain use directions for Florigraze perennial peanuts must be amended to refer to this crop as "'Florigraze' rhizoma peanuts" or "'Florigraze' perennial (rhizoma) peanuts."

- According to the BEAD use pattern table (Residue Chemistry chapter 08/11/04), at least one fluazifop-P-butyl product includes uses on nonbearing ginseng, olive, and/or small fruits. All labels which include these uses must be modified to specify that the crop may not be harvested for food/feed use within one year of treatment.

- Also according to the BEAD use pattern table, at least one fluazifop-P-butyl product lists a maximum seasonal rate of 0.75 lb ai/A for soybean. The affected label(s) must be modified to specify a maximum seasonal application rate of 0.5 lb ai/A to soybeans, to be consistent with the registrant's labels.

- According to the BEAD use pattern table, at least one fluazifop-P-butyl product lists a 14-day post-harvest interval (PHI) for pecans. The affected label(s) must be modified to specify a 30-day PHI for pecans, to be consistent with the registrant's labels.

- The rotational crop restriction on the product labels for EPA Reg. Nos. 100-1071 and 100-1116 which prohibits the grazing of rotated small grain crops and the harvesting of these crops for livestock forage and straw is impractical and must be removed.

2. New plant metabolism studies, with a root crop and a leafy vegetable, must be submitted.

3. New livestock metabolism studies, with ruminants and poultry, must be submitted.

4. The tolerance enforcement methods must be radiovalidated in conjunction with the required plant and animal metabolism studies.

5. The registrant must submit a regulatory method for poultry eggs.

6. Additional storage stability data are needed for the following commodities: asparagus, carrot, coffee, cotton meal, cotton hulls, cotton refined oil, peppers, soybean meal, soybean hulls, soybean refined oil, stone fruit, prunes, sweet potato, poultry tissues, and eggs. Additional storage stability data are needed to support the required crop field trial and processing studies.

7. Additional crop field trial data are required for asparagus, carrot, cotton seed, cotton gin byproducts, and dry bulb onion.

8. A coffee processing study must be submitted.

9. New confined rotational crop studies must be submitted.

10. The available analytical reference standard for the resolved isomer of fluazifop has expired (2/03). An updated certificate of analysis or a new lot of standard must be submitted.

10.2 Occupational and Residential Exposure

HED has no data to assess exposures from applications using a sprinkling can. Therefore, ORETF residential hose-end data were used in the assessment as a surrogate.

11.0 References

Fluazifop-p-butyl. Revised Acute and Chronic Dietary Exposure Assessments for the Tolerance Reassessment Eligibility Decision (TRED). PC Code:122809. DP Barcode: D310695. Sherrie L. Kinard. December 8, 2004.

Fluazifop-P-butyl. Report of the Metabolism Assessment Review Committee. PC Code: 122809. DP Barcode: 298939. Sherrie L. Kinard, David Anderson, and William P. Eckel. July 8, 2004.

Fluazifop-p-butyl: REVISED Residential Exposure Assessment and Recommendations for the Tolerance Reassessment Eligibility Decision (TRED) Document. Margarita Collantes. November 29, 2004.

Fluazifop-P-butyl. Revised TRED - Report on FQPA Tolerance Reassessment Progress and Interim Risk Management Decisions. Residue Chemistry Considerations. Case No. 2285. Sherrie L. Kinard. December 8, 2004.

Review of Fluazifop Butyl Incident Reports. DP Barcode D299665. Chemical#122805 and 122809. Jerome Blondell and Monica S. Hawkins. March 10, 2004.

Tier 1 Drinking Water Assessment for Fluazifop-p-butyl. William P. Eckel. October 29, 2004.

Tier 2 Drinking Water Assessment for Fluazifop-P-butyl and its Major Degradate Fluazifop-acid. William P. Eckel. June 30, 2004.

APPENDIX 1.0 TOXICOLOGY DATA REQUIREMENTS

Test	Technical	
	Required	Satisfied
870.1100 Acute Oral Toxicity	yes	yes
870.1200 Acute Dermal Toxicity	yes	yes
870.1300 Acute Inhalation Toxicity	yes	yes
870.2400 Primary Eye Irritation	yes	yes
870.2500 Primary Dermal Irritation	yes	yes
870.2600 Dermal Sensitization	yes	yes
870.3100 Oral Subchronic (rodent)	yes	yes
870.3150 Oral Subchronic (nonrodent)	yes	yes
870.3200 21-Day Dermal	yes	yes
870.3250 90-Day Dermal	no	yes
870.3465 90-Day Inhalation	no	yes
870.3700a Developmental Toxicity (rodent)	yes	yes
870.3700b Developmental Toxicity (nonrodent)	yes	yes
870.3800 Reproduction	yes	yes
870.4100a Chronic Toxicity (rodent)	no	yes [a]
870.4100b Chronic Toxicity (nonrodent)	yes	yes
870.4200a Oncogenicity (rat)	yes	yes
870.4200b Oncogenicity (mouse)	yes	no [b]
870.4200b Oncogenicity (hamster)	no	yes
870.4300 Chronic/Oncogenicity	yes	yes
870.5100 Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300 Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5xxx Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a Acute Delayed Neurotox. (hen)	no	yes [c]
870.6100b 90-Day Neurotoxicity (hen)	no	- [c]
870.6200a Acute Neurotox. Screening Battery (rat)	no	-
870.6200b 90 Day Neuro. Screening Battery (rat)	no	-
870.6300 Develop. Neuro	no	
870.7485 General Metabolism	yes	yes
870.7600 Dermal Penetration	no	yes
Special Studies for Ocular Effects [d]		
Acute Oral (rat)	-	-
Subchronic Oral (rat)	-	-
Six-month Oral (dog)	-	-

[a] Guideline 870.4300 satisfies this requirement. [b] The study in the hamster satisfies this requirement. [c] Required for organophosphates only. [d] Reserved.

APPENDIX 2.0 NON-CRITICAL AND CRITICAL TOXICOLOGY STUDIES

All Executive Summaries of studies submitted are not presented below. Only the Executive Summaries of acceptable studies and/or those not already discussed in the hazard assessment and the endpoint selection sections are presented. Although all submitted studies were considered, Executive Summaries of studies which did not alter the risk assessment and/or were considered unacceptable are not included (See Table 4.1d for a listing).

2.1 Subchronic Studies

2.1.1 Subchronic Studies in Rats with Fluazifop-butyl

EXECUTIVE SUMMARY: In a 90-day oral toxicity study (MRID 00093820) [fluazifop-butyl (94.8% a.i., batch/lot #P14; Ref.#C4916, 3/4/79)] was administered to 20 Wistar rats/sex/group in the diet at dose levels of 0, 10, 100 or 2000 ppm (equivalent to 0, 0.7, 7.1, 144.5 mg/kg bw/day for males and 0, 0.8, 8.0, 161.9 mg/kg/day for females, measured dosage from food consumption).

There were no clinical signs or deaths during the study. Body weight (11%) and body weight gain(14%) were decreased in males at 2000 ppm. Food consumption (19%) was increased and a slight reduction of food efficiency (28%) were seen in males at 2000 ppm only. These parameters were nominally affected in males, but none were affected in females.

The hematology parameters PCV (4%), Hb (4%) at 2000 ppm and RBC count (3% at 100 ppm and 6% at 2000 ppm) were statistically significantly decreased at the indicated doses in males only, at 11 weeks. Similar changes were noted in males at 5 weeks, but since the change was small and did not change with study duration, the changes may have been related to factors other than a direct toxicity of the test compound.

Clinical chemistry parameters show effects at 2000 ppm and sometimes at 100 ppm in males. At 2000 ppm and 5 weeks, alkaline phosphatase (AP) (55%) and alanine transaminase (ALT) (32%) was statistically significantly elevated only in males and at 11 weeks, alkaline phosphatase (74%) and alanine transaminase (40%) were elevated. Cholesterol (28% and 31%)) and total protein (6% and 6%) were statistical significantly depressed, respectively, at 100 ppm and 2000 ppm at week 5 in males. Similar depressions, in total protein and cholesterol were seen in males at 11 weeks. Cholesterol was depressed significantly only in males. Except for a albumin depression of 5% and 12% at 100 ppm and 2000 ppm, respectively, and ALT increase of 22% at week 11, no similar findings were reported for females.

At necropsy in the 2000 ppm group, slight relative liver weights (48%) and kidney weights (11%) were statistically significantly increased in males and in females absolute (9%) and relative liver weight (10%) were increased. Absolute testes weight (30%) was statistically significantly increased at 2000 ppm, but ovarian weights showed no change. Neither relative testes weight nor relative ovarian weight was changed.

Histologically, in control, 10, 100 and 2000 ppm groups, males showed 0/20, 0/20, 16/20 and 20/20, respectively hepatocellular findings. At 100 ppm, there were 16/20 males with slight or moderate hepatocytic hypertrophy (all areas). At 2000 ppm, there were 13 of 20 males

with of slight or moderate hepatocytic hypertrophy (all areas), 4 of 20 males with moderate hepatocytic hypertrophy (all areas) with vesicular nuclei, 3 of 20 with moderate hepatocytic hypertrophy with vesicular nuclei and/or necrosis. The total hepatic findings were 16/20 at 100 ppm and 20/20 at 2000 ppm (each animal finding counted once). Slight, moderate and marked kidney cortical tubular degeneration was seen at 100 ppm (4/20) and 2000 ppm (12/20). Control showed 2 of 20 males with similar kidney degenerations. Females showed slight periacinar small vacuolation 6/20 at 2000 ppm. No treatment related findings were reported histologically for either the testes or ovaries.

The minor elevations in liver enzymes are considered biologically significant only when considered in conjunction with the liver histopathology in males at 100 and 2000 ppm. Kidney histopathology was seen at 100 (4/20) and 2000 (13/20) ppm as increased slight, moderate and marked cortical tubular degeneration. The dose related cholesterol depressions were statistically significant and may have been biologically significant. Although the total protein concentration was also depressed at 100 and 2000 ppm in males and females and is consistent with the liver effects at 2000 ppm, the protein depressions were within experimental range.

The LOAEL is 100 ppm (7.1 mg/kg/day), based on liver and kidney histopathology and cholesterol depression in males and 2000 ppm (162 mg/kg/day) in females based on absolute and relative liver weight increase and marginal 22% elevated ALT and depressed albumin. The NOAEL is 10 ppm (0.7 mg/kg/day) for males and 100 ppm (8.0 mg/kg/day) for females. The study authors also considered these NOAEL/LOAELs as appropriate.

This 90-day oral toxicity study in the rat is acceptable (guideline) study and satisfies the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3100; OECD 408) in the rodent species. The conclusions take precedence over previous conclusions in TXR# 001982, although the LOAEL/NOAEL are unchanged.

2.1.2 Subchronic Study in Rats with fluazifop-P-butyl

EXECUTIVE SUMMARY: In a 90-day oral toxicity study (MRID 46158402]), fluazifop-P-butyl (batch/lot #P12; 95.9% [RS, mixture] and 93% [R, isomer], and batch/lot #P8; 93.8% [RS, mixture] and 92% [R isomer]) was administered to 20 Alpk/AP Wistar rats/sex/group in the diet at dose levels of 0, 10,100 or 2000 ppm (equivalent to 0, 0.5, 5, or 100 mg/kg bw/day).

In a confirmation study, 40 additional male Alpk/AP Wistar rats were studied at identical doses and duration (CTL study# PR0612). In this second study, 20 males/group were sacrificed at 5 weeks and 13 weeks. Kidneys were weighed at 5 weeks and 13 weeks and at week 13, 20 rats/group were grossly examined and the kidneys examined histologically. .

In the initial study, male body weights were decreased (18%) and food consumption decreased (13%) and food efficiency (g body weight gain/g food consumption) (5%) were statistically significantly decreased at 2000 ppm. No decrease was seen in female body weight, food consumption or food efficiency.

There were dose related statistically significant decreases in hemoglobin concentration, hematocrit and red blood cell counts (8%-10%) at week 5 and 2000 ppm and (4%-14%) at week 13 and 100 ppm and 2000 ppm in males. There was no reported correlation with the histology.

Clinical chemistry showed increased in plasma alkaline phosphatase, alanine transaminase and aspartate transaminase values which were dose related (13% to 100%) at 100 ppm and 2000 ppm. Although these values show some enzyme leakage from liver cells, no liver pathology was reported. The study authors suggested that only metabolic induction occurred. At 5 weeks, alkaline phosphatase was elevated 15% at 100 ppm and 29% at 2000 ppm; the remaining enzymes were elevated only at 2000 ppm at week 5 (37% to 100%). Total plasma protein was decreased 5% to 7% at week 5 and 13. Cholesterol was decreased at all dose level at week 5 and week 13 (13% to 52%).

Organ weights showed some changes. Absolute and relative liver weight were increased at the top dose level in males. Absolute testes weight showed a statistically significant dose related decrease at all dose levels (4.9% to 6.6%) when "outlier" weights were removed. The relatively flat dose response showed a reduced relative weight that was statistically significantly reduced, but less than the next lower dose. Absolute and relative spleen weights showed a dose related statistically significant decrease in males (9.5% to 24%) and females (9 to 15%) at termination at the two top dose levels. Relative kidney weights were statistically increased at the top dose in males and females, but not absolute kidney weights. Absolute and relative brain weights were increased (2.9%) in females at the 2000 ppm.

Histologically, livers were swollen in males at the top dose. The incidence and severity of kidney tubular nephropathy was marginally increased in males and females at the two top doses.

In the repeat 90-day study in males only, this apparent dose relationship kidney histopathology disappeared. In the repeat study in males, controls showed tubular nephropathy equivalent to higher dose levels in incidence and grade. The incidence at higher doses was similar in both studies. Thus the repeat study showed that nephropathy was commonly seen in these Wistar rats as early as 90-days. It was also noted that the kidneys were probably stressed as shown by the repeat study showing statistically significant absolute and relative kidney weight increase at 5 and 13 weeks at 2000 ppm.

The LOAEL is 5 mg/kg/day, based on decreased spleen weight in males and females and decreased hemotological parameters in males. At 2000 ppm male body weight was decreased and kidney weight increase. The NOAEL is 0.5 mg/kg/day. However, there is statistically significant testes weight decrement and cholesterol depression at all dose levels.

This 90-day oral toxicity study in the rat is **ACCEPTABLE (GUIDELINE)**; and does satisfy the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3100; OECD 408) in the rodent species.

2.1.3 Subchronic Study in Hamsters with Fluazifop-P-butyl

EXECUTIVE SUMMARY: In a 90-day oral toxicity study (MRID 46082902) Fluazifop-p-butyl (91.6% a.i., Batch No. P23) was administered to 12 Golden Syrian Lak [LVG(SYR)BR)] hamsters/sex/dose in the diet at concentrations of 0, 250, 1000, or 4000 ppm (equivalent to 0, 19.5, 78.3 or 291.9 mg/kg/day for males and 0, 19.9, 79.0 or 319.6 mg/kg/day for females respectively).

There were no toxicologically significant compound-related effects on mortality, hematology, urinalysis, clinical signs, organ weights or gross pathology, although male hemoglobin concentration and hematocrit were lower (9% - 10%) and male plasma sodium was 3% lower, phosphorus was16% lower at 4000 ppm compared with control. Male brain weight was increased (4%), adjusted male liver weight was increased 28%, adjusted kidney weight in males and females was increased (22%-10%), epididymal weight was decreased 22%, and testes weight was reduced 16% at 4000 ppm compared with control. Hematology, clinical chemistry and organ weight values were statistically different, $p< 0.05$ to $p<0.01$, at 4000 ppm compared with control. Toxicity was evident at the 4000 ppm dietary level in males from lower body weight (-14%; $p\leq 0.01$ at termination) and body weight gain (-31% at termination) as well as decreased food efficiency ($p\leq 0.05$: weeks 1-4). Evidence of liver toxicity in both sexes at this dietary level included centrilobular eosinophilia/loss of glycogen, as well as slightly lower total plasma protein ($p\leq 0.05/0.01$: m/f). The brain, kidneys, testes and epididymides showed no treatment related histological findings.

The LOAEL for Fluazifop-p-butyl in hamsters is 4000 ppm (291.9 and 319.6 mg/kg/day in males and females, respectively) based on suppressed body weight/body weight gain and decreased food efficiency in males and evidence of liver toxicity: centrilobular eosinophilia/loss of glycogen in males and females. The NOAEL is 1000 ppm (78.3 and 79.0 mg/kg/day in males and females, respectively).

This 90-day oral toxicity study in the is **Acceptable/Guideline** [the study report indicated that this is a range-finding study] and satisfies the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3100; OECD 408) in the hamster.

2.1.4 Subchronic Studies in Dogs with Fluazifop-butyl

EXECUTIVE SUMMARY: In a 90-day oral toxicity study (MRID 00093821), PP009 [fluazifop-butyl, 99.6% a..i., batch/lot# P17; CTL Ref# Y00083/001/008] was administered to 4 Beagle dogs/sex/group in gelatin capsules at dose levels of 0, 5, 25 or 250/125 mg/kg/day (with 0.4 ml corn oil vehicle/kg) for 13 weeks. The 250/125 mg/kg/day group received the 250 mg/kg/day dose for 30 days, at which time the dosage was reduced to 125 mg/kg/day for the remainder of the 13 weeks (2 males and 1 female) were killed due to severe ulcerations of cornea prior to 30 days). Saw dust bedding was used on the kennel floor.

At 250 mg/kg/day, the three dogs (2 males and 1 female) killed prior to day 30 started to show signs in the eye at day 22. Th eye lesions progressed rapidly to ulcers of the cornea; in the most severely affected dog the iris was protruding through the cornea by day 25 day (day of sacrifice). These three dogs lost weight before sacrifice. Their relative liver, kidney and adrenal weights were higher than in the dogs treated for 13 weeks. Histological examination of these

dogs showed treatment related lesions of the eye, gastrointestinal tract, livers and testes. Ulceration and/or inflamation were present in esophagus, duodenum, ileum, caecum and colon. Oil-Red-O positive moderate periacinar fatty degeneration and hepatocytic hypertrophy was seen in these three dogs.

Body weight gain in males (53%) and females (60%) dogs that survived the 250/125 mg/kg/day dose to week13, showed lower body weight gain than controls (page 29 of 00093821). Male dogs showed a significant weight loss week 4 to 13 (-1.0 kg) at 125/250 mg/kg/day. Female dogs showed no body weight gain or loss over the same time period. Dogs in the other groups showed weights comparable with control animals. Food consumption at 250/125 mg/kg/day, was only nominally less than other groups. Food efficiency in the 250/125 mg/kg/day group was also nominally less in males (98% of control) and females (95% of control) [page 28 of 00093821]. Food consumption in other groups was comparable with control.

Platelet counts in males were depressed in the 250/125 mg/kg/day group at the day 27 and day 84 determinations (58% to 42% in males, respectively) and 32% in females at day 27, which returned to normal by day 84. The remaining groups were variable, but comparable with control. Clinical chemistry data showed that the elevated AP (44%), ALT (172%) and AST (56%) in surviving males in the 250/125 mg/kg/day group at day 27 (the first day of measured values) had returned to normal by the end of the study. Females that showed elevations in ALT (143%) at day 27 and (213%) at day 55, but was returning toward normal by day 84 (61%).

One surviving male at 250/125 mg/kg/day showed brightly yellow colored urine after week 4 and 8 and one surviving female at 250/125 mg/kg/day showed brightly colored yellow urine at week 4. In the urine of these surviving males and females, increased number of epithelial cells were found, but no bile. Organ weights were normal.

At Histological examination, the testes of the 2 surviving males at 250/125 mg/kg/day showed "diffuse maturation arrest of the germinal epithelium with occasional spermatid giant cell formation." No dose related histopathology was seen in other groups, except in the dogs dosed at 250 mg/kg/day that were killed for humane reasons at 1 month .

The LOAEL is between 250 and 125 mg/kg/day in both males and females based on multiple pathology in 3 dogs (2 males and 1 female) that were killed at 1 month for humane reasons. They showed body weight loss, severe eye lesions, gut lesions and hepatotoxicity. In surviving dogs, significant body weight loss, with slight reduced food efficiency, platelet count increases, and liver enzyme elevations suggesting reversing hepatotoxicity in surviving animals. In addition, in the 2 surviving males, maturation arrest of the germinal epithelium of the testes was seen. The NOAEL was 25 mg/kg/day.

This 90-day oral toxicity study in the dog is acceptable (guideline); and satisfies the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3150; OECD 409) in non-rodent species. The NOAEL/LOAEL is not changed from TXR# 001982.

2.1.5 21-Day Dermal Study in Rabbits with Fluazifop-butyl

EXECUTIVE SUMMARY: In a 21-day dermal toxicity study (MRID 00093819 & 92067017), PP009 fluazifop-butyl, 99.6% a.i., batch/lot# P17)] was applied to the shaved skin of 5 unabraded and 5 abraded New Zealand White rabbits/sex/group at dose levels of 0, 100, 500 or 2000 mL/kg or about, 6 hours/day for 5 days/week during a 21-day period.

Male and female rabbits died at 500 and 2000 mg/kg/day. One male at 500 mg/kg/day died on day 21. At 2000 mg/kg/day, 4 males died or were killed in extremis from day 6 to 8 and 5 females died or were killed in extremis from day 7 and 10. The report authors stated that the cause of death could not be determined. However, the timing of the deaths are consistent with kidney failure, but there was minimal evidence that kidney failure was related to the deaths. In 3 animals killed in extremis, blood urea was increased 3 fold in one animal and 2 fold in 2 animals, but in the animals that survived no increase in blood urea was noted. All but one animal of the animals that died or were killed in extremis showed proteinaceous material in Bowman's spaces of the glomerulus of the kidney, which probably suggests compromised kidneys, but the severity was not graded. Since, this is a frequent finding in rabbits, the significance of finding the proteinaceous material in the kidney was discounted in the report. However, the finding appeared to be more frequent in these unscheduled dead animals. Another finding in animals that died was red or dark brown "abnormal" contents frequently in the caecum of 8 of the 10 unscheduled dead animals, but also in the remaining gastrointestinal tract of some of these animals. None of animals that survived to day 21 showed abnormal contents in the caecum. Marked decrease in erythrocytes and platelet counts with extreme elevation in normoblasts (some in mitosis) and slight depression of white cells were noted 2 animals that were killed in extremis. The remaining animals that died showed a slight depression in erythrocyte counts. No consistent, dose related clinical signs were reported in the surviving rabbits. In rabbits that were killed in extremis or died, body weight loss and reduced food consumption including a number of signs, such as diarrhea, inactivity and pallor of mucus membranes was noted.

The body weights of the animals that died or were killed in extremis lost weight (10 to 22%), refused to eat 2-5 days before death and showed lower food consumption (11 to 112 g/day versus 144 to 169 g/day in surviving animals).

Only mild dermal irritation was noted at the beginning of test material application in all groups with no biologically significant difference among groups. No differences were noted in systemic effects or irritation between unabraded and abraded rabbits.

For systemic toxicity, the LOAEL is 500 mg/kg/day, based on death in one male and at 2000 mg/kg/day death of 4 males and 5 females. No biologically significant difference from controls in irritation. The NOAEL is 100 mg/kg/day.

This 21-day dermal toxicity study in the rabbit is **ACCEPTABLE (GUIDELINE)** and satisfies the guideline requirement for a 28-day dermal toxicity study (OPPTS 870.3200 ; OECD 410) in rabbits. The study acceptability and NOEL/LOAEL were not changed from TXR# 001982. These conclusions take precedence over previous conclusions in TXR# 001982.

2.2 Chronic and Carcinogenicity Studies with Fluazifop-butyl and fluazifop-P-butyl

2.2.1 Chronic Study in Dogs with Fluazifop-butyl

EXECUTIVE SUMMARY: In a chronic toxicity study (MRID 00131462, 00131463, 92067018) fluazifop-butyl, PP009 (99.6% a.i., batch/lot # P17)] was administered to 6 Beagle dogs/sex/group in 0.4 ml corn oil/kg in a gelatin capsule at dose levels of 0, 5.0, 25, or 125 mg a.i./kg/day for 55 weeks. Food consumption and body weight were recorded weekly; physical examination was recorded every 4 weeks and ophthalmoscopy 10 times. Hematology and blood chemistry measurements were made from all animals on study week 0, 4, 8, 13, 16, 21, 25, 38 and 50. Routine uranalyses were made on all animals on week 0, 8, 17, 27 and 39. Bone marrow myelograms were studied at week 10 from the femur head or iliac crest from control and high dose and at week 52 from all dogs prior to sacrifice. At necropsy, the sternum of all dogs was examined at week 55. Necropsy and microscopic examination were conducted on all animals that died or were killed in extremis and at termination and organ weights were taken at termination.

At 125 mg/kg/day 5/6 males were killed in extremis between week 9 and 52-55 and 2/6 females were killed in extremis between week 29 and 49. A primary condition resulting in the animal being killed was not stated, but most of these dogs showed subdued behavior, inappetance 4 to 14 days before death, body weight loss, reduced erythrocytes counts, decreased hemoglobin concentration and decreased packed cell volume, increased liver and spleen weights, bile excretion in the urine and lymphadenopathy. Histopathology on these animals showed hypercellular bone marrow, extra medullary hematopoiesis in the spleen, ulcers at all levels of the gastrointestinal tract, cataracts and thymus involution in 5 males and 2 females along with various other lesions. Cortical vacuolation of the adrenals and vacuolation of the liver in 4 males and 2 females were seen. Testes in 3 of these males showed tubular degeneration. Other signs in some of these animals include pallor, palpable spleens, tremors, mydriasis and icterus. Bloody stools were reported for only one high dose male. Body weight loss was consistently seen among decedent males and females and the most consistent histological finding among these animals was lesions in the gastrointestinal tract.

Body weight was variable, but in the dogs that survived to terminal sacrifice, males (1/6) and females (4/6) body weights at 125 mg/kg/day were not different from control weight at termination. Dogs in the 5 mg/kg/day group tended to be similar to control, while dogs in the 25 mg/kg/day group tended to be lower than the 5 mg/kg/day group and the control.

Treatment related eye lesions occurred at 125 mg/kg/day only. Vacuolation and/or cataracts were seen 4/6 males and 4/6 females at 125 mg/kg/day. Incidental findings were shown in other groups, but none were considered test material related lesions.

Hematology in the 125 mg/kg/day group showed effects starting at week 4. Platelet counts were decreased by 67% in males and 32% in females; RBC counts were decreased 10% in males and 8% in females; packed cell volume (PCV) was decreased 10% in males and females. Males showed statistically significantly lower RBCs at 25 (10%) only on week 38. The decreased RBCs at 25 mg/kg/day were within historical control range and were discounted. At 125 mg/kg/day the values remained around these levels or showed no significant change at termination at week 50.

Other than an increased incidence of hypercellularity in bone marrow myelograms at

125 mg/kg/day, no other blood related affects were considered biologically significant at lower doses. The statistically significant elevations of meta-myelocytes and statistically significant decreases in segmented cells that occurred at all doses in the myelograms from the iliac crest or femoral head were discounted because the increase and decrease were small, variable and not considered treatment related and comparable with historical controls. The hypercellularity of sternal bone marrow was detected histologically at terminal sacrifice only in males that were killed in extremis and in 2 surviving females at 125 mg/kg/day and in 1 control female. Of all the cells studied from the bone marrow of the iliac crest or femoral head, meta-myelocytes and segmented neutrophil cells were the only ones showing statistical significance, but no dose relationship. Bone marrow myelograms that were prepared at week 10 and week 52, included 17 cell types of the myeloid series and 4 of the erythroid series. The statistic used to show differences, Student's "t" test, is not appropriate for multiple comparisons. The increased meta-myelocyte neutrophils are not accompanied by changes in hematology at 5 and 25 mg/kg/day including differential white blood cell counts.

At week 50 and 125 mg/kg/day, clinical chemistry showed increased alkaline phosphatase (AP) in males (150%) and females (114%), increased alanine amino transferase (ALT) in males (107%) and females (162%), increased lactic dehydrogenase in males (237%), decreased cholesterol in females (42%) and at 25 mg/kg/day decreased cholesterol in females (16%). Also at 125 mg/kg/day the % bromosulphalein (BSP) retention was increased in males (320%) and females (113%), but not at 25 mg/kg/day. These increased and decreased values were statistically significant at $p < 0.01$ or < 0.001. At no time interval were plasma enzymes significantly increased at 25 mg/kg/day.

Statistically significantly difference in organ weights were seen only in female kidneys at 125 mg/kg/day. Absolute (26%) and relative (21%) female kidney weights were increased significantly at 125 mg/kg/day and the one surviving males showed a kidney weight increase of 12%. Livers were nominally elevated in 1 surviving male and surviving females at 125 mg/kg/day, in addition to the weight increases in decent males and females. Apparent dose related decreased spleen weights were seen in surviving dogs at all dose levels. Due to the large standard deviation in spleen weights in the control dogs, the decreased spleen weights at all dose levels were not statistically significant and the relevance to treatment is unknown. However, **increased** spleen weights were stated to be one of the characteristics among decent dogs killed in extremis. These **increased** spleen weights among decedent dogs and **decreased** spleen weights among surviving dogs were not explained, but may be another example of the variation in individual animals effects seen with fluazifop-butyl administration in other studies. Testicular tubular degeneration in 3 dogs may have been treatment related, but testes volume and weight were nominally decreased at 125 mg/kg/day, but due to the lack of surviving males, potential effects were not demonstrated.

Significant treatment related histological findings occurred mostly in the dogs in the125 mg/kg/day group that died or were killed in extremis. However, increased incidence of adrenal cortical fatty vacuolation was seen in surviving females scheduled for terminal sacrifice at greater or equal to 25 mg/kg/day (4/4 surviving females at 125 mg/kg/day and 3/6 females at 25 mg/kg/day versus 2 in control (2/2 showed this vacuolation in decedent females). The incidence of thymic involution may have been treatment related at 25 mg/kg/day, since 1/6 showed slight thymic involution at 25 mg/kg/day, females 2/2 decedent females showed thymic involution, 3/4 surviving females showed the effect at 125 mg/kg/day. No thymic involutions

were seen in the 5 mg/kg/day group or control females. Thymic involution was seen in 5/5 decedent males, none in the surviving male, 2/6 dogs at 25 mg/kg/day and 3/6 dogs in control, 1 of which was severe.

The LOAEL is 25 mg/kg/day based on marginally increased incidence of adrenal cortical fatty vacuolation in females and increase incidence of thymic involution in females and at 125 mg/kg/day death of 4/6 males and 2/6 female dogs, eye lesions and lesions of the gastrointestinal tract, adrenal vacuolation, thymic involution and bone marrow hypercellularity in males and females. The NOAEL is 5 mg/kg/day.

This chronic study in the dog is ACCEPTABLE (GUIDELINE); and satisfies the guideline requirement for a chronic oral study [OPPTS 870.4100, OECD 452] in the dog. Although the NOAEL/LOAEL may not be definitive (based on adrenal vacuolation, one of which was the same female dog showing the slight thymic involution), it is unlikely that a repeat study would show a lower LOAEL. In addition, the results of this study are consistent with the results from the 90 day subchronic dog study (MRID# 00093821), such as reduced body weight, gut lesions, liver enzyme increases and reduced platelet counts at 125/250 mg/kg/day, but no evidence of spleen weight changes. The conclusions on the NOAEL/LOAEL of 5/25 mg/kg/day in TXR# 003846 were not changed, however, the reasons for the NOAEL/LOAEL were changed and take precedence over previous conclusions. The increase in meta-myelocytes neutrophils and decreased segmented neutrophils in the bone marrow myelograms were discounted in a memorandum from Whang Phang, dated 7/17/86 (HED file code 21110 HIARC Briefing Pkgs). Syngenta's response to questions about the chronic dog study answered ambiguities in the study [Meeting Notes and Response from Syngenta (May 17, 2004) to Carmen Rodia].

COMPLIANCE: Signed and dated G.P., Quality Assurance, and Data Confidentiality statements were provided. Several problems were seen with the study. (1) Analyses of urine from the dogs as proof of absorption was incomplete and inadequately described and analyses/ methodologies were not under adequate analytical control (standard deviations of the data exceeded means). In contrast, a metabolism study in dogs (MRID# 00093829) conducted in a different laboratory after the chronic study, the urine analyses were found to be well controlled and reliable (Standard deviations were much less than the mean)(See Section F, Analyses of the urine for fluazifop acid metabolite). (2) The colony of dogs (Alderly Park beagle dogs) used in the study appeared to excessive health problems, such as partially collapsed lung lobs, bronchitis, pleurisy, enlarged/prominent congested lymph nodes, parasitic granulomas and other health problems possibly sporadically affecting some of the study results. (3) Homogeneity and stability were not reported, but concentrations of fluazifop-butyl used in capsules administered to the dogs were satisfactory.

2.3 Delayed Neurotoxicity in Hens with Fluazifop-butyl

EXECUTIVE SUMMARY: In a delayed neurotoxicity study (MRID 00093818) [fluazifop-butyl (98.6% a.i., batch/lot #P23)] was administered to 5 domestic hens/group by corn oil gavage at dose levels of 0, or 15000 mg/kg to determine a LD50. In the delayed neurotoxicity portion of the study, fluazifop-butyl was administered similarly to 10 hens/group at 0, 3750, 7500 or 15000 or 15000 mg/kg. The latter groups were followed for 21 days; clinical signs were noted and histological examination of the brain, spinal cord and sciatic nerve of the birds was conducted.

A known delayed neurotoxin, trichloro-ortho-cresyl phosphate (TOCP) was administered at 500 mg/kg as a positive control.

In the LD50 study, 2 of the 10 birds dosed at 15000 mg/kg died or were sacrificed in a moribund condition. One bird died on day 16. Birds lost an average of 428 g during the 21 day observation period.

During the neurotoxicity assessment, weight change for the control, 3750 mg/kg, 7500 mg/kg and 2- 15000 mg/kg groups was + 78 g, -34 g, -139 g, -480 g and -450 g, respectively. No neurotoxic signs were noted during the 21 days of the study. Two of the 20 birds in the two 15000 mg/kg groups showed generalized muscular atrophy, 1 showed an enlarged spleen and 1 showed opalescent and a thickened epicardium Histopathology of the nervous system showed no dose related lesions, while the TOCP dosed birds showed the expected results. **Fluazifop-butyl exposed hens show no evidence of delayed neurotoxicity in the hen.**

The study is ACCEPTABLE(GUIDELINE) acute delayed neurotoxicity study in hens (81-7). The conclusions were not changed from TXR# 001982.

2.4 Metabolism and Pharmacokinetics in Rats with Fluazifop-butyl

EXECUTIVE SUMMARY: In multiple studies on metabolism (MRID 00093822, 00093823, 00093824, 00093825, 00093826, 00093827, 00093828) Wistar rats were dosed (singly and multiply with different concentrations of radio-labeled PP009. To the extent possible these individual studies will be summarized to give a complete description of the multiple studies represented by the above MRID#s. [PP009; fluazifop-butyl, 97.4 %a.i., uniformly radio-labeled in phenyl group] was administered to Wistar male and female rats in single oral doses of 1 mg/kg and 1000 mg/kg, single intravenous (iv) doses of 1 mg/kg and multiple 14 day doses of 1 mg/kg. Excretion in the urine and feces was measured over a 7 -10 day period. Excreted compounds were measures in the urine, feces and bile. Tissue residues were measured at the end of the 7-10 day period. Blood levels and one-half lives were measured at various times and under several dosing regimens.

Blood one-half lives ranged from 2.7 hours from the iv 1 mg/kg dosed females to 43 hours from the 1000 mg/kg dosed males (See MRID 00093828).

In summary of all the individual metabolism studies, it is clear that fluazifop-butyl is rapidly absorbed through the gut and ester linkage is hydrolyzed rapidly to PP009 acid {2-(4-[5-(trifluromethyl)-2-pyridinyloxy]phenoxy] propionic acid} in the blood stream (See MRID 00093828).

This would suggest that the toxic effects of PP009 are due to PP009 acid. In addition, the longer retention time in males may also be partly responsible for the greater toxicity to males than females.

Qualitatively the metabolites do not differ in males and female, but there are minor quantitative differences. PP009 acid is major metabolite and with its conjugates essentially the only metabolite of importance (See MRID 00093822, 00093824, 00093825, 00093826 and

00093827). Minor amounts of the ether cleavage products appear in the urine and feces, generally <0.7%. Parent PP009 is found in the feces (0.6% to 68%) of males and females depending on the dosing regimen, but not in urine of males or females. [The small amount found in the urine of females in one study could have been due to contamination.] The bile of males contains 20 times the amount of PP009 acid and its taurine conjugate as the bile of females, which shows that bile excretion in the female is minor compared with the male (See MRID 00093824).

Low dose (1 mg/kg) (MRID 00093824) and high dose (1000 mg/kg) (MRID 00093825) male and female rats show similar qualitative metabolic profiles, which show minor quantitative differences.

In the repeat dosing studies, males showed a much lower % of parent excreted in the feces 4.5% as compared with the parent at 50.5% in the single dose study. Females did not show the same degree of difference, but the difference was in the same direction (MRID 00093826).

The combined metabolism study reports (MRID 00093822, 00093823, 00093824, 00093825, 00093826, 00093827 and 00093828) are acceptable (guideline) and satisfy the requirements for PP009 metabolism in rats (85-1). The guidelines had not been finalized when these studies were conducted.

2.5 Comparative Metabolism in Rats of Fluazifop-butyl and Fluazifop-P-butyl

EXECUTIVE SUMMARY: The purpose of this special study (MRIDs 00162445 and 00162446) was to compare the metabolism of fluazifop-butyl, which is a 50:50 mixture of R and S enantiomers, with PP005, which is a mixture containing predominately the R enantiomer (90:10). In this study, [U-Phenyl-^{14}C] fluazifop-butyl (Test substance no.: Y00083/005/009; radiochemical purity: 96.1-96.7%) or [U-Phenyl-^{14}C] PP005 (Test substance no.: Y00083/025/001 and Y02746/004/002; radiochemical purity: 93.9-96.8%) in corn oil, was administered to Wistar-derived rats (2-6 of one sex in each of 10 groups) as a single gavage dose at 1 mg/kg and 1 MBq/kg. Samples were collected from these animals to determine elimination kinetics and to identify and quantify metabolites.

Overall recovery was 86-93% dose from all treated animals. Although there were clear differences based on sex, the pharmacokinetics and metabolism of fluazifop-butyl and PP005 were similar. For each sex, the quantity of the radioactivity found in cage wash, urine, feces, bile, selected tissues (fat, kidney, and liver), and blood were similar regardless of treatment. During the first 2 days post-dose, 69-81% dose in females and 38-40% dose in males was recovered as the R and S enantiomers of fluazifop in the excreta of all treated animals. The concentration (µg equiv./g) of fluazifop in the blood was generally similar in animals treated with fluazifop-butyl or PP005, indicating the lack of a preferential absorption of a particular enantiomer. The results of the quantification of the R and S enantiomers in the excreta suggest that there is an *in vivo* conversion of the S enantiomer into the R enantiomer in the absorbed dose. Regardless of sex or the racemic mixture (fluazifop-butyl [50:50] or PP005 [90:10]), the R:S enantiomer ratio in the blood one hour or more after dosing was approximately 97:3, corroborating the evidence found in the urine. Furthermore, this ratio of enantiomers in the blood was constant throughout sampling (up to 24 hours post-dose for males and 12 hours post-

dose for females). These data suggest that the toxicity would be similar in rats treated with either fluazifop-butyl or PP005 at 1 mg/kg.

Absorption (based on radioactivity recovered in the urine) was extensive in females (75-89%), but was less so in males (49-51%). Furthermore, excretion in the urine was rapid in females, 66-83% dose within 1 day post-dose. Conversely, excretion was slower in males, largely taking place over a 3 day period post-dose in urine (41-43% dose) and feces (26-27% dose). Results from the biliary study suggested that 25-34% dose was not absorbed in males. Over the 7 day post-dose period, relatively little of the dose was excreted in the feces of females (3-11%), while 35% dose was excreted in the feces of males. Radioactivity in the tissues and cage wash of each sex was <=1% dose.

Tissue residues were less in females than males. For the tissues sampled, the concentration of radioactivity was highest in the fat (0.40-0.67 µg equiv./g in males and 0.05-0.07 µg equiv./g in females). In the kidney, liver, and blood, radioactivity was 0.07-0.21 µg equiv./g in males and <=0.01 µg equiv./g in females.

The data showed some variability suggesting individual animal variability in excretion rate and route of excretion. However, the portion ascribable to experimental variation or individual animal variation could not be determined. Other studies (MRID# 00093822, 00131455, 00131464 and 41563704) on the metabolism of fluazifop-butyl in rats and humans suggest some individual variation.

This study is classified as **acceptable/non-guideline** and satisfies the purpose for which it was intended.

2.6 Plasma Level Time Course for Fluazifop-butyl and Fluazifop-P-butyl in Rats

EXECUTIVE SUMMARY: Fasted male and female Alpk:APfSD (Wistar derived) rats were gavaged (MRID# 46082910) with 200 mg/kg ^{14}C-labeled fluazifop-p-butyl or fluazifop-butyl (90:10 and 50:50 R:S ratio, respectively). Rats were sacrificed and blood was collected from 3 rats/sex at 15 minutes, 30 minutes, and 1, 2, 3, 4, 5, 6, 12, and 24 hours after dosing into tubes containing the plasma esterase inhibitor paraoxon (100 µg/mL plasma). HPLC was used to determine plasma levels of fluazifop-ester [RS] and its metabolite fluazifop acid. No parent fluazifop-ester was detected in plasma at any time point. Only the R-isomer of fluazifop acid was detected in animals given Fluazifop-p-butyl, whereas both the R and S isomers of fluazifop acid were detected in rats given Fluazifop-butyl. At >5 hours after dosing, however, only the R isomer of fluazifop acid was detected in plasma of rats treated with either test material. The rate of elimination of the acid metabolite was similarly rapid for the two test materials. Metabolite levels were greatest 4-6 hours after dosing, thereafter declining similarly in males and females except at the 24-hour time point, when males had 9 to 50-fold greater remaining metabolite levels than females. This study obtained results similar to a previous experiment in which rats were gavaged with 1 mg/kg of fluazifop butyl or fluazifop-p-butyl, with the exception that in the previous study only the R-isomer of fluazifop acid was detected in plasma treated with either test material, whereas the present study found appreciable amounts of the S-enantiomer in plasma from animals treated with fluazifop-butyl, at least for the first 5 hours after dosing.

This study is **Acceptable/Nonguideline**. It provides useful information about the plasma level time course of fluazifop-p-butyl and fluazifop-butyl in the rat. The study would be more complete and robust upon providing additional information in the study report, as detailed in the "Deficiencies" section. However, the study compliments other extensive previous studies on blood levels of the acid metabolite at lower doses and contributes to the time course of the metabolite isomers in rats.

2.7 Absorption, Excretion in Hamsters Administered Fluazifop-P-butyl

EXECUTIVE SUMMARY: Two studies were conducted, phase 1 and phase 2, using separate groups of male and female hamsters [MRID# 46082923]. In phase 1, hamsters (4/sex/dose) were gavaged with a 1:10 water dilution of diets containing 200, 750, or 3000 ppm [^{14}C] fluazifop-p-butyl (10 mL/kg). The hamsters were then fed a diet containing unlabeled test material for 3 days and sacrificed. Urine, cage wash, and feces were collected 12, 24, 36, 48, and 72 hours after dosing, and the blood and tissues were collected 72 hours after dosing and the radioactivity counted. In phase 2, hamsters (3/sex/dose/time point) were acclimatized to a reversed 12 hour light/dark cycle and were fed diets containing 200 or 3000 ppm [^{14}C] fluazifop-p-butyl as soon as the dark cycle began and continuing for 4 to 24 hours, when they were sacrificed. Several groups fed ^{14}C-diets for 24 hours were kept another 12-36 hours and fed diets containing unlabeled test material.

Elimination by phase 1 animals was rapid, as 72-82% of the administered radioactivity was excreted by males, and 82-88% by females within 12 hours of dosing. Over the 72-hour collection period, the majority of the radiolabel was excreted in the urine (70-83% for males; 76-93% for females) and feces (11-24% for males; 10-16% for females), irrespective of dose. The phase 1 animals had low levels of radiolabel in the tissues and carcasses (0.18-0.43% of the given dose). The greatest concentration of radioactivity (µg equivalents fluazifop-p-butyl/ g tissue) was in abdominal fat in both sexes (up to 0.036 µg/g in males and 0.026 µg/g in females), and 750 and/or 3000 ppm males also had low but measurable radiolabel in the kidneys, liver, prostate, blood, plasma, and carcass (up to 0.022, 0.016, 0.013, 0.001, 0.004, and 0.013 µg/g, respectively). The low tissue radioactivity precluded determining a clear pattern of distribution among the organs and differences between the sexes. The total recovery of radioactivity including urine (with cage washes), feces, GI contents, tissues, and carcass was 92.6-103.4% for all but one animal.

The phase 2 males and females had similar patterns of tissue radioactivity over time, levels at 3000 ppm being roughly 10 to 30-fold greater than at 200 ppm. Males typically had 2-fold greater radioactivity levels than females for any given tissue and time point. The greatest concentrations of radioactivity in 3000 ppm males was in the prostate, plasma, liver, blood, and kidneys (up to 496, 74.7, 73.8, 67.3, and 49.3 µg/g, respectively), and in the females was in the ovaries, uterus, blood, kidneys, liver, and plasma (up to 47.3, 46.6, 38.6, 35.2, 34.5, and 34.3 µg/g, respectively). Radioactivity levels reached steady-state by 4-8 hours of treatment, but dropped precipitously at the 36-hour time point (12 hours after exposure ended) in all tissues except the liver (dropped at 48 hours) and abdominal fat (was relatively constant across time). Two distinct peaks of tissue radioactivity levels were seen in 3000 ppm males, and particularly in 200 ppm females, the dip occurring at 16 hours. The study author speculates that the two peaks were due to two distinct periods of dietary consumption during the 24-hour exposure period.

HPLC analysis and mass spectroscopy of plasma and liver samples showed the presence of only one metabolite, fluazifop acid. Levels of fluazifop acid in plasma paralleled radioactivity levels across time. The 0-72 hour AUC for fluazifop acid for males was 32.8 and 1426.8 hrμg/g at 200 and 3000 ppm, respectively, and for females was 23.3 and 666.1 hrμg/g, respectively. This indicated that males had a greater systemic exposure to fluazifop and its metabolite fluazifop acid than females.

This study is **Acceptable/Nonguideline**. The study provides useful information concerning the elimination, absorption, distribution, and metabolism of Fluazifop-p-butyl in hamsters. The study report has a number of shortcomings that should be addressed for this study to be considered robust and complete (see Deficiencies section).

2.8 Absorption, Excretion and Tissue Retention in Mice Administered Fluazifop-butyl

EXECUTIVE SUMMARY: Male and female mice (3/sex) were gavaged with 1 mg/kg [phenyl- ^{14}C] PP009, and females (6/group) were gavaged with 150 mg/kg [phenyl- ^{14}C] or [pyridine- ^{14}C] PP009 (5 mL/kg)[MRID# 46082925]. Urine (+ cage wash) and feces were collected at 24-hour intervals for 7 days for the low-dose groups, and at 24 and 48 hours for the high-dose groups. Urine radioactivity was counted directly by liquid scintillation (LSC), whereas fecal and tissue samples were homogenized and combusted/oxidized prior to LSC. The samples were extracted with methanol, an aliquot hydrolyzed in 6 M HCl, and the contents separated by thin layer chromatography (TLC) using silica gel plates.

Mice dosed with 1 mg/kg [phenyl- ^{14}C] PP009 excreted ~79% of the administered radiolabel in the urine and feces within 48 hours, and >94% by 7 days after dosing. Males excreted somewhat more radioactivity in the feces and females excreted more in the urine. Females dosed with 150 mg/kg PP009 excreted only 25.5-43.6% of the administered radioactivity in the urine and feces within 48 hours, and tended to excrete more label in the feces. The greatest concentration of radioactivity was in abdominal fat in both sexes. The same eight metabolites, in roughly the same relative amounts, were found in the urine and feces of males and females given 1 mg/kg [phenyl- ^{14}C] PP009. Metabolites #1 (the PP009 acid taurine conjugate) and #5 (PP009 acid) accounted for most of the radioactivity in the urine (61.4-80.2% and 14.4-27.7%, respectively) and feces (33.3-45.9% and 46.3-47.0%, respectively). Following hydrolysis, levels of metabolite #1 decreased in the urine (1.3-2.9%) and feces (1.5-3.5%) whereas levels of metabolite #5 increased (63.1-77.6% and 73.3-74.5% in urine and feces). TLC of urine samples using another solvent system showed that metabolite #1 included two minor unidentified metabolites, which were not seen after acid hydrolysis. Females given 150 mg/kg [phenyl- ^{14}C] or [pyridine- ^{14}C] PP009 generally had a similar spectrum and distribution of urinary and fecal metabolites as those given 1 mg/kg [phenyl- ^{14}C] PP009. One exception was that metabolite #4 (2-(5-trifluoromethyl) pyridone) was not found in mice dosed with [phenyl- ^{14}C] PP009, and metabolite #3 (2-(4-hydroxyphenoxy) propionic acid) was not found in females given [pyridine- ^{14}C] PP009, which may have been due to detectable radiolabel adding to the sensitivity [but this was not made clear].

Individual animal variation in the amount excreted by the mouse as well as the rat, dog and human was seen. Some of the variation may have been due to variation in the analytical analyses.

This study is **Acceptable/Nonguideline**. The study provides useful information concerning the excretion and metabolism of PP009, but is not a definitive evaluation. A second confirmatory analytical method (e.g. HPLC, GC) is needed and the deficiencies noted (see Deficiencies section) should be addressed for this study to be considered robust and complete.

2.9 Absorption and Excretion Studies in Dogs with Fluazifop-butyl

EXECUTIVE SUMMARY: In a metabolism study (MRID 00093829)([C^{14}]PP009, 97.4% a.i., uniformly labeled in the phenyl ring only) and PP009, 100% a.i. were administered to 3 Beagle dogs/sex in a single dose in corn oil by capsule at a dose level of 1.0 mg/kg. Excreta were collected for 5 days and % radiolabel excreted determined, except day 3 when the feces were accidently discarded. Blood samples were collected at 0.25, 0.5, 1, 2, 4, 6 and 24 hrs after dosing. After the 5 days dogs were killed and tissue samples analyzed for residual radioactivity. Potential biliary excretion was not determined.

The rate of excretion of PP009 in the urine and feces was essentially the same for males and females. This is in marked contrast to rats where excretion rate in females was much more rapid than in males. In male dogs, 32.8% and 40.2% of the dose administered was excreted in the urine and feces, respectively, within 5 days. In female dogs, 40.7% and 41.5% of the administered dose was excreted in the urine and feces, respectively, within 5 days. Total recovery in the urine, feces and cage washes from males was 73.5% of the dose administered and in the same parameters from females was 83.2 % of the dose administered. Within the first 48 hours in males, 30.7% and 39.0% of the administered dose was excreted in the urine and feces, respectively. Within the first 48 hours in females, 39.0% and 40.9% of the administered dose was excreted in urine and feces, respectively.

The metabolic products were similar in males and females, qualitatively and quantitatively. Only 2 products were detected in urine and 3 in feces. Similar to rats, a polar metabolite in urine and feces remained at the chromatographic origin (not identified)(12% in males and 8% in females). The PP009 acid was the major metabolite in the urine of males (79%) and females (86%) and in the feces of males (81%) and females (76%) of extractable material. PP009 parent was detected only in feces of males (4.5%) and females (5.5%) of extractable material. The radiolabel was not detected in blood after 5 days and only small amounts were detected in the liver, kidneys and fat of males and females.

Peak blood levels in males and females were about the same at 0.5 - 2 hours, excluding the female with delayed absorption. One female dog failed to show significant blood levels for about 1-2 hours after dosing, and showed a maximum blood level 4-6 hours after dosing. An explanation of this delayed absorption was not given in the report. The approximate one-half life of the label in the blood of males and females, excluding the one female with delayed absorption, appeared to be about 2 hours.

The study is ACCEPTABLE (NON-GUIDELINE) study of metabolism in dogs.

2.10 Peroxasome Proliferation in Mice, Rats, Hamsters, *In vitro* and *In vivo,* and Humans, *In vitro*, Administered Fluazifop-P-butyl

EXECUTIVE SUMMARY: An *in vivo* and *in vitro* study [MRID 46082919] was conducted to assess the ability of Fluazifop-p-butyl (94.0% a.i., Lot No. Y02746/115) to increase peroxasome proliferation and hepatocyte replication. Fluazifop-butyl (93.9% a.i., Lot No. Y00083/001/043) was used also in the *in vivo* studies to verify the Fluazifop–p-butyl results. The species involved were mouse, rat, hamster and human. The *in vitro* study exposed hepatocyte cultures from rats, mice, hamsters and humans to Fluazifop-p-butyl at dose ranges of 25-2000 µM. The first *in vivo* test exposed 3 males and 3 females per group of Alpk:APfSD rats, C57BL10J mice and Golden Syrian hamsters to Fluazifop-p-butyl in feed at concentrations of 0, 80, 250, 500, 1000, 1500 or 2000 ppm and Fluazifop-butyl at concentrations of 0, 80, 250 or 1000 ppm for 10 consecutive days. The second test exposed 5 males and 5 females per group of Alpk:APfSD rats to Fluazifop–p-butyl at 0, 80, 250, 1000 or 2000 ppm and Fluazifop-butyl at concentrations of 0 or 2000 ppm in feed for up to 56 days.

The hepatocyte cultures were prepared, exposed to the Fluazifop-p-butyl (25-2000 µM) and incubated. Peroxasome proliferation occurred in the animal tissue with mouse hepatocytes exhibiting the strongest response. This proliferation was dose-related in the animals tested. No response was noted in the human cultures.

The 10 day feeding study data were consistent with the *in vitro* study exhibiting an increase in peroxasome proliferation upon exposure to Fluazifop-p-butyl. Mice showed the greatest response with no gender differences; male mice had proliferation increases from 5.1-fold at 250 ppm to 8.3-fold at 2000 ppm. Females ranged from 2.1-fold increase at 250 ppm to 9.0-fold at 2000 ppm. Rats had a significant dose-related increase in males only ranging from a 2.7-fold to 12.4-fold increase at 80 and 2000 ppm, respectively. Female rats had no significant increases. Female hamsters showed a slight but statistically significant increase in proliferation in the 2000 ppm group only. Male hamsters exhibited no increase in any group. Similar trends were reported in the Fluazifop-butyl exposure.

The 56 day feeding study showed an increase in proliferation in male rats and a less pronounced trend in the females following exposure to Fluazifop-p-butyl. Males showed an increase of 2.2-fold at 80 ppm and 9.8-fold at 2000 ppm. Females ranged from no increase in proliferation at 80 ppm to a 1.5-fold increase at 2000 ppm. Similar trends were reported in the Fluazifop-butyl exposure.

There was no increase in hepatocyte cell replication in any of the animals or human tissue. This was true for the *in vitro* and *in vivo* studies. The positive control, epidermal growth factor, did show appropriate cell replication verifying the ability of cells to replicate.

These studies are **Acceptable/Nonguideline** and conclude that Fluazifop-p-butyl increases peroxasome proliferation in rats, mice and hamsters but not human tissue. Hepatic cell replication did not occur in any of the animal or human tissues. Hepatic cell replication did not occur in the rats in the feeding study either.

2.11 Androgen/Estrogen Activity with Fluazifop-P-butyl, Fluazifop-butyl and the Acid Metabolites

EXECUTIVE SUMMARY: In an *in vitro* study [MRID 46082916], recombinant

Saccharyomyces cerevisiae yeast strains containing either the human estrogen or androgen receptor were exposed to fluazifop-p-butyl (94.0% a.i., Lot No. Y02746/115), fluazifop-butyl (93.9% purity, a.i., Lot No. Y00083/001/043) and their respective acids (chemically synthesized from parent compounds).

Positive control agonists utilized were 17ß-estradiol (estrogenic) and dihydrotestosterone (DHT-androgenic), and positive control antagonists utilized were hydroxytamoxifen (for estrogen) and flutamide (for androgen). Negative control compounds were also utilized: nicotinamide, Hepes and ascorbate.

Saccharyomyces cerevisiae yeast strains had DNA sequences encoding the human estrogen (ER) or androgen (AR) receptors incorporated into their genome. The yeast strains also contained plasmids carrying ER and AR responsive elements controlling the reporter gene, LacZ, which encodes the enzyme ß-galactosidase. If interaction occurred with either estrogen or androgen, the ß-galactosidase would interact with a chromogenic substrate (CPRG) and create a color change that could be measured by absorbance. Failure to interact would result in no color change. In determination of the anti-estrogenic or anti-androgenic (antagonist) activity, the natural ligand (17ß-estradiol and DHT) were added to the appropriate assay medium.

At concentrations up to 1 mM, fluazifop-p-butyl (FpB), fluazifop-butyl (FB), FpB-acid and FB-acid did not exhibit any estrogenic, androgenic, anti-estrogenic or anti-androgenic activity in the yeast strain. Positive agonists, positive antagonists and negative controls reacted appropriately.

This *in-vitro* study testing estrogenic and androgenic activity is **Acceptable/Nonguideline** and resulted in **no evidence of estrogenic or androgenic activity**.

2.12 Multidose Dermal Study in Humans with Fluazifop-butyl

EXECUTIVE SUMMARY: In a dermal absorption and pharmacokinetic study (MRID 46082908), fluazifop-butyl (97.4% a.i., Lot No. Y00083/043/003) was administered to 6 male humans topically on the back once daily in 5 consecutive doses of 20 mg (0.025 mg/cm^2 of skin). The dosing solution was an aqueous dilution of commercial formulation, JF6901, with a fluazifop-butyl concentration of 0.5%.

Four milliliters of the dosing solution was evenly applied to an 800 cm^2 area of the back. After the solution dried, a study t-shirt was worn. Eight hours after exposure, the t-shirt was collected. The exposure site was washed and the wash water collected. Another study t-shirt was worn overnight. Volunteers showered the next morning and again the study t-shirts were collected. Study t-shirts and wash water were analyzed for fluazifop-butyl concentrations.

The amount of fluazifop-butyl recovered from the total amount applied (100 mg) was 85.5 ± 8.4% (calculated mean ± s.d.). The majority of the applied fluazifop-butyl was recovered from study t-shirts worn by participants (72% of the original dose) and water collected from washing (10%). Based on these results, less than 5% of the original dose applied was absorbed into the body

Plasma concentrations were measured in all subjects at multiple time-points using GC-

MS analysis to determine the presence of fluazifop-butyl's main metabolite, fluazifop. The results showed increases with each exposure with the peak at the 120 hour time point. Levels dropped off quickly once dosing was terminated. Results supported the conclusion that fluazifop does not accumulate in the body.

Urine was collected at multiple time-points and analyzed for pH, creatinine, total volume, and fluazifop concentration. The pH, total volume and creatinine results were within normal limits. The metabolite fluazifop was measured in the urine with GC-MS analysis. Results of the study showed fluazifop-butyl is rapidly metabolized into fluazifop and excreted in the urine.

No treatment-related toxicities were seen on dermal absorption of fluazifop-butyl. Although only a small amount of the applied amount was absorbed, rapid metabolism into the metabolite, fluazifop, and urinary excretion occurred.

It is noted that the urinary output of fluazifop acid increased with plasma levels over the 5 day dosing period, but did not show evidence of significant accumulation. The slight increase in plasma and urine levels were consistent with the daily dosing and the estimated 15 hour one-half-life based on excretion. Estimates of one-half-lives varied from 12.6 to 17.3 hours, which do not suggest as wide a variation as other human studies showing delayed absorption and excretion.

This 5- day dermal absorption study in human is **Acceptable/Nonguideline** and satisfies the study's intent.

2.13 Oral Absorption and Excretion in Humans with Fluazifop-butyl

EXECUTIVE SUMMARY: In a metabolism study (MRID 00131464)(Fluazifop-butyl, 99.6% a.i, Y00083/012/003) were administered to 3 male humans in a single dose in corn oil on a sugar cube at a dose level of 0.07 mg/kg. [Whether the test material was the [RS] or [R] material was not stated nor were the reference numbers given repeated in other studies] Excreta were collected for 7 days and blood samples were collected every ½ hour up to 4 hours and hourly to 8 hours, and at 24 hour intervals up to 168 hours (7 days). The amount of fluazifop (free acid) excreted in the urine was determined on daily samples. Although determination of the test material/metabolites in feces was listed in the protocol, no feces were collected within the 7 days of the study except one sample from one subject. The one-half life of fluazifop-butyl was calculated from the free acid in blood and urine samples. Peak plasma levels and plasma binding were determined. Clinical examinations and chemistries on the 3 subjects were conducted before and after dosing and daily for 7 days. The dosage was based on expected exposures from preliminary findings in workers spraying fluazifop-butyl. The limit of detection in plasma and urine was the same at 0.01 mg/L

The results from the study were consistent with the studies in rats and dogs. That fluazifop-butyl is rapidly absorbed, hydrolyzed to the free acid and excreted mostly in the urine as the free acid, with minor amounts of conjugates of the free acid (conjugates unidentified in humans). The one-half life in the men studied was closer to that found in female rats, which lacked the delayed excretion characteristic of males rats possibly being due to biliary recycling in male rats.

Data on the one-half lives was measured from plasma decrease and urinary excretion of fluazifop acid. The mean one-half life from plasma for subject 1 and 2 was 12 and 13 hours, respectively, with indeterminate/variable data from both of the subjects being consistent with another shorter one-half life of about 5-9 hours, but the data was too variable for meaningful t ½ determinations. Two distinct one-half lives were shown by the data from the plasma of subject 3 (t ½~ 5 and 37 hours). The one-half life from urine showed single compartment kinetics of t ½ ~ 11 hours for subject 1 and t ½ ~ 9 hours for subject 2. The one-half life from urine for subject 3 was 18-21 hours. Peak levels of the free acid were seen about 1 to 2.5 hours in plasma and in the first 24 hour urine collection after dosing.

If the toxicity of fluazifop-butyl is related to delayed excretion time seen in male rats, then the rapid excretion in men in the current study may suggest that the toxicity in men is more closely related to the dog and female rats where the excretion time is also short. In toxicity studies in rats, toxicity in males was always more severe than in females.

Only hydrolyzed fluazifop-butyl or the free acid was detectable in plasma and the free acid and its conjugate were detected in urine. The excretion of the test material was complete within 7 days, with plasma levels being undetectable within 72-144 hours (3-6 days) and with urine levels being undetectable at 96-144 hours (4-6 days).

Total recovery of fluazifop as the conjugate and the free acid in the urine from each of the 3 men were 80%, 93% and 92% (Mean 88.3%) of the dose and 1-4%, 6% and 23% as a conjugate, respectively. [It was assumed that the total recovery reported included conjugated fluazifop acid, but this was not completely clear. The values calculated by the reviewer not including the conjugates show higher results for subject 2 and 3 (Table 3) than calculated by the study authors (Table 3). Since calculation by the authors were not completely clear and could not be verified for this reason, the study authors % recovery are presented here.] Feces were analyzed from subject 1, only. He yielded another 0.8% of the dose as the free acid. Since the recovery was only 0.8%, the feces of the remaining subjects were not analyzed. Binding to plasma was high and consistent, being 95.0% to 95.8% in dosed subjects and 95.4% to 96.0% in 3 undosed subjects.

The study is ACCEPTABLE(NON-GUIDELINE) study of metabolism in humans dosed orally.

The study supplied useful information, but it was not a complete metabolism study in humans. The study is upgraded from "not applicable" in TXR# 003846 to "acceptable/nonguideline". The conclusions in the current executive summary takes precedence over pervious conclusions.

2.14 Dermal Penetration in Humans with Fluazifop-butyl

EXECUTIVE SUMMARY: In a dermal absorption and Pharmacokinetic study (MRID# 46082918), six men (age 18-45; weight 60-90 kg)/dose were dosed dermally with 2 mg and 200 mg of 0.05% or a 5.0% (w/v) solution of fluazifop-butyl in a Fusalide® formulation with a break of approximately one month between each concentration. Four ml of the solution was spread over 800 cm^2 of the backs of the 6 men, allowed to dry and left uncovered for 8 hours. Plasma and urine was collected in multiple samples over a 264 hour period. Plasma was collected

hourly for 4 hours, every 2 hours for 12 hours and every 24 hours to the end. Urines were collected every 4 hours for 12 hours and then every 24 hours to the end. The application site was washed after 8 hours with water using cotton swabs and 3%Teepol and covered with a T-shirt over the application site until morning. At 24 hours after application the site was again washed with a 3% solution of Teepol. The washes, T-shirts, plasma and urine samples were analyzed for fluazifop-butyl or fluazifop acid. The study was conducted with volunteers. An experienced medical practitioner was available throughout the study.

Most of the applied dose appeared to be on the surface of the skin and easily removed. Recovery of test material was good, a mean of 93.4% ± a standard deviation of 13% at the 2 mg dose and mean of 83.2% ± a standard deviation of 21% at the 200 mg dose. Peak plasma levels were shown to occur 24 to 31 hours after application in these men. The one half life for excretion was about 18 hours. In arriving at these percentages of recovery the study author's added a correction to the amount excreted in the urine up to 120 hours, i.e., to the amount excreted up to 120 hours was added the amount excreted after 120 hours through a 2 compartment pharmacokinetic model. However, this latter correction was insignificantly small amounting to about 0.008% of the 200 mg applied to the skin. In arriving at the dermal absorption percentage, the study author's corrected the recovery by three factors, 1.17 [the ratio of the mole weight fluazifop-butyl and fluazifop acid], 100/91 [the amount of recovery from thawed frozen urine (no supporting data was presented)] and 100/90 [the recovered urinary fluazifop acid from a oral study in humans (supported by MRID 00131464)]. This later factor was used to correct for residual material in skin, organs and other tissue, which would require similar test subjects in both studies for which there is not evidence.

The study author's calculated the percentage absorption to be 8% at the 2 mg dose and 1.6% at the 200 mg dose.

The current reviewer modified the study author's percentage absorption. The modified dermal absorption was calculated by two methods; (1) Unrecovered added to absorbed material, and (2) Scaling recovered material to100%. Method (1) yielded absorption factors of 18.4% and 14.6% at the 2 mg dose and 200 mg dose, respectively. Method (2) yielded absorption factors of 8.6% and 1.9% at the 2 mg dose and 200 mg dose, respectively.

Method (2) appeared to be more reasonable because residual material (unrecovered) may have been relatively immobile. The unrecovered test material was speculated to be in the outer layers of the skin and appeared to be easily removed.

Human oral studies with fluazifop-butyl show rapid excretion of fluazifop acid in the urine and almost no excretion in the feces of humans (MRID# 00131464). Oral dog and female rat studies show similar results, which were similar to human oral studies. Male rats show similar fluazifop acid excretion to the female, but excretion is slower because fluazifop is excreted in the bile, resulting in a higher % in the feces of males rats. Residual fluazifop acid appears to be retained in the body fat (<1% to 8% in the rat) and speculated to be esterified to mono or diglycerides. This small amount of residual material if released, was too low to be accurately detectable in the urine. Since multiple dosing studies show that fluazifop-butyl does not accumulated in the body and is not a carcinogen. This residual material is relatively immobile and may be toxicologically insignificant. Thus, the scaling of the recovered material to100% or method (2) may supply an appropriate dermal absorption factor.

In conclusion, the dermal absorption factors are 8.6% and 1.9% for the dermal dose of 2 mg and 200 mg, respectively.

The study is ACCEPTABLE(NONGUIDELINE); there is no guideline for a dermal absorption study in humans. The 1991 study was not conducted under GLPs.