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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: 12/21/05

MEMORANDUM

SUBJECT: **Fluthiacet-methyl:** Human Health Risk Assessment for Proposed Use on Cotton. PC Code: 108803, Petition No: 7F4821, DP Barcode: D269687, Decision # 301228

Regulatory Action: Section 3 Registration Action
Risk Assessment Type: Single Chemical Aggregate

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Herbicide Branch
Registration Division (7505C)

DEC 29 2005

Introduction

The Office of Pesticide Program's (OPP) Health Effects Division (HED) is tasked with estimating the risk posed to human health from exposure to pesticides. Previously, OPP's Registration Division (RD) asked HED to evaluate Syngenta's (as Agent for K-I Chemical USA, Inc.) petition to grant fluthiacet-methyl tolerances in/on cotton raw agricultural commodities (Petition No. 7F4821, 1997). Upon review, HED determined there were data deficiencies that precluded granting these tolerances (Petition No. 7F4821, D234717, D234495, D238930, D239384, D249645, D257126, W. Wassell 2/20/2001). Subsequently, K-I Chemical submitted additional data and requested that the Agency continue its review and processing of the fluthiacet-methyl tolerances on cotton. Furthermore, they requested an amendment to EPA Reg. No. 63588-8, Appeal™ EC, adding the harvest aid/defoliant use in/on cotton (a formulation registered for use on soybeans and corn).

This document provides a summary of the findings from the data evaluation and the subsequent assessment of human health risk resulting from the proposed use of fluthiacet-methyl on cotton. The hazard assessment and characterization was conducted by Meta Bonner (RAB3); the occupational exposure assessment was performed by Barry O'Keefe (RAB3); chemistry data evaluation was conducted by Michael Doherty (RAB2); the risk and dietary exposure assessments were conducted by Sarah Winfield (RAB3) and the drinking water assessment was provided by Keara Moore and Mary Frankenberry of OPP's Environmental Fate and Effects Division (EFED).

Provided revised Sections B (proposed labels) and F (proposed tolerances), with the modifications specified in Section 10.0 of this document, are submitted, the residue chemistry and the toxicological databases support the establishment of a conditional registration and permanent tolerances as follows:

Tolerances for combined residues of fluthiacet-methyl and its acid metabolite CGA-300402:		
Cotton, undelinted seed	0.02	ppm
Cotton, gin byproducts	0.20	ppm

HED recommends that conversion of conditional registration to unconditional registration may be considered upon resolution of the deficiencies specified in Section 9.0.

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1.0 Executive Summary

Syngenta (as Agent for K-I Chemical USA, Inc.) previously petitioned the Agency to grant fluthiacet-methyl tolerances in/on cotton raw agricultural commodities (Petition No. 7F4821, 1997). Upon review, the Agency determined there were data deficiencies that precluded granting these tolerances. Subsequently, K-I Chemical submitted additional data and requested the Agency continue its review and processing of the fluthiacet-methyl tolerances on cotton (*i.e.*, for residues of fluthiacet-methyl and its acid metabolite CGA-300402 in/on gin trash at 0.500 ppm [they did not propose a tolerance for residues in/on cotton seed]). Furthermore, K-I Chemical requested an amendment of EPA Reg. No. 63588-8 for Appeal™ EC (10.3% fluthiacet-methyl/active ingredient [ai]), adding the harvest aid/defoliant use in/on cotton (a formulation registered for use on soybeans and corn). The following human health risk assessment addresses this request.

Use Profile
The fluthiacet-methyl formulation Appeal™ is an emulsifiable concentrate (EC) and is proposed for application via ground and aerial equipment on cotton at relatively low application rates (0.0043 - 0.0064 lb ai/A, up to twice per season, maximum seasonal application rate 0.0089 lb ai/A). The use of Appeal™/fluthiacet-methyl on cotton will be marketed as a harvest aid/defoliant, and therefore application and harvest activities are fairly proximal (proposed pre-harvest interval [PHI] is 3 days).

Hazard Profile
The fluthiacet-methyl toxicology database, reviewed previously by the HED Hazard Identification Assessment Review Committee (HIARC), indicates adverse effects generally affect the liver and erythropoietic system, and that it has low acute toxicity. No appropriate endpoint attributable to a single dose (exposure) was identified in oral toxicity studies, and therefore, an acute dietary assessment was not conducted. Conversely, a chronic dietary assessment was conducted, and the quantitative hazard estimate employed in the assessment is based on liver toxicity observed in the 18-month carcinogenicity study in the mouse. No hazard was identified for short- and intermediate-term dermal exposure durations, since no localized or systemic toxicity was seen at the limit dose in the 28-day dermal toxicity study in the rat (coupled with a lack of susceptibility and neurotoxicity in the fluthiacet-methyl toxicology database), and therefore, these risk assessments were not conducted. However, since the 28-day dermal study does not evaluate the potential effects of long-term exposure, the same quantitative hazard estimate used in the chronic dietary assessment is used in the long-term dermal assessment, along with a dermal absorption factor, newly identified by the HED Registration Action Branch 3 (RAB3) Toxicology Team. Also newly featured in this assessment are inhalation quantitative hazard estimates (also selected by the RAB3 Toxicology Team), which are currently required due to guidance changes since the last risk assessment was completed. The short- and intermediate-term inhalation quantitative hazard estimates are based on adverse effects observed in the blood and liver in the 90-day oral toxicity study in the rat. Fluthiacet-methyl is classified as "likely to be a human carcinogen," and consequently, a cancer risk assessment was conducted using a linear low-dose approach (Q_1*) based on male mouse combined (adenomas/carcinomas) liver tumor rates.

Aggregate Risk
Since there are no registered nor proposed residential uses of fluthiacet-methyl, aggregate risk is

limited to dietary (food and water) exposure. Furthermore, since no appropriate endpoint attributable to a single dose was identified in oral toxicity studies, only chronic and cancer aggregate risks were determined. Fluthiacet-methyl residue estimates on food and water were included directly into the dietary model DEEM-FCID™. The assessment is partially refined (with percent crop treated information), yet conservative, because actual exposure is expected to be low: usage data indicates less than 1% of field corn, sweet corn and soybean crops are treated with fluthiacet-methyl, and field trial data indicates when crops are treated, residues are either not detected or detected at low levels. The overall chronic dietary risks from residues in foods are less than 1% of the chronic Population Adjusted Dose (cPAD) for the general U.S. population. The most highly exposed population subgroup is all infants < 1 year, which occupies 1.4% of the cPAD. These risk estimates are very low, and do not exceed HED's level of concern (HED is concerned when estimated dietary risk exceeds 100% of the PAD). The overall cancer dietary risk for the U.S. population is 7.51×10^{-7}, which does not exceed HED's level of concern (HED is generally concerned when estimated cancer risk exceeds one in one million [*i.e.*, the risk exceeds 1×10^{-6}]).

Occupational Risk

Chemical-specific handler exposure data were not submitted in support of this action. Nevertheless, inhalation exposure and risk assessments to fluthiacet-methyl were conducted for open mixing/loading and applying liquids for open-cab groundboom application and enclosed cockpit aerial application, as well as while flagging for aerial application. These assessments were conducted using PHED (The Pesticide Handler Exposure Database, Version 1.1, Surrogate Guide, August 1998) unit exposure values. With only baseline clothing, the non-cancer inhalation risk estimates for all handler scenarios were not of concern (*i.e.*, resulted in margins of exposure [MOEs] well above HED's level of concern of ≤100). On the other hand, occupational cancer risk estimates (amortized dermal and inhalation exposure) did result in certain scenarios with risks between 10^{-6} to 10^{-4}. For the scenario of aerial applications, cancer risk levels of 10^{-6} or less were not achieved for mixers/loaders or applicators, even with the addition of full personal protective equipment (PPE) and engineering controls. Since aerial application scenarios failed to achieve cancer risk levels of 10^{-6} or less at the maximum application rate (which was used since typical application rates were not provided), the lower application rate of 0.0043 lb ai/A (the low-end of the application rate range provided on the label) was also used to calculate cancer handler risk estimates, *i.e.*, for risk management purposes. However, cancer risk levels of 10^{-6} or less were still not achieved for mixers/loaders, even with the addition of full PPE, but were achieved for applicators using engineering controls. For those scenarios where the estimated handler cancer risks are in the 10^{-6} to 10^{-4} range it would be warranted to seek ways of cost-effectively reducing risks, such as increased levels of personal protection, as is commonly applied with non-cancer risk estimates (*i.e.*, additional PPE or engineering controls - adding gloves gives the most significant reduction in exposure).

The restricted entry interval (REI) under the Worker Protection Standard (WPS) is based on the acute toxicity of technical grade fluthiacet-methyl, which is classified in acute toxicity category III/IV. Acute toxicity category III chemicals require a 12-hour REI. Thus, the 12-hour REI that appears on the Appeal™ EC label is appropriate under the WPS. Per the WPS, the minimum level of PPE is based on the acute toxicity of the end-use product. RD is responsible for ensuring the PPE listed on the label is in compliance with the WPS.

In addition to the WPS-established REI, an REI was also calculated for the cancer risk associated with fluthiacet-methyl. Only dermal exposures were assessed because once sprays settle, inhalation exposure is not expected, and therefore, the inhalation postapplication route of exposure is not relevant. Postapplication risks were assessed for workers entering cotton fields to conduct scouting activities. The cancer risk for scouters on the day of application is 4.3×10^{-7}, using the maximum application rate. Therefore, the postapplication cancer risk does not exceed HED's level of concern.

Overall, there is no risk concern for chronic and cancer aggregate exposures, nor for non-cancer occupational exposures. However, there is a cancer risk concern for occupational workers either mixing and loading fluthiacet-methyl for aerial application, or aerially applying fluthiacet-methyl, without additional PPE and/or engineering controls.

2.0 Ingredient Profile

References:

Fluthiacet-methyl. Petition for the Establishment of Tolerances for Use on Field Corn, Sweet Corn, Pop Corn, and Cotton. Submission of Residue Analytical Method, Multiresidue Method, and Crop Field Trial Data for Cotton. PP#7F4821, Michael Doherty, 11/22/05, D304795.

Pesticide Fact Sheet: Fluthiacet-methyl, USEPA, April 1999, http://www.epa.gov/opprd001/factsheets/fluthiacet.pdf

2.1 Summary of Registered/Proposed Uses

Fluthiacet-methyl is an herbicide in the imine chemical family. Of relevance to this document, is the fluthiacet-methyl emulsifiable concentrate (EC) Appeal™ (10.3% ai, EPA Reg. No. 63588-8). The registrant is requesting an amendment to the Appeal™ label, to add the harvest aid/defoliant use on cotton. Appeal™ is currently registered for use as a selective postemergence herbicide for control of velvetleaf and other broadleaf weeds in corn and soybeans. The proposed use on cotton is presented in Table 2.1.

Table 2.1 Summary of Directions for Use of Fluthiacet-Methyl on Cotton.

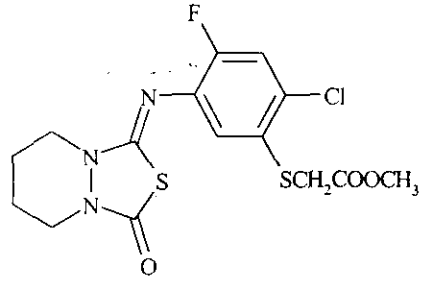
Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Cotton						
Postemergence broadcast foliar ground or aerial	0.91 lb ai/gal EC [63588-8]	0.0043-0.0064	2	0.0089	3	Aerial application is to be made in a minimum of 3 gal/A and ground application is to be made in a minimum of 10 gal/A. A minimum retreatment interval of 6 days is proposed.

Application can be made via aerial or ground sprays, and is to be made only: (1) after all bolls to be harvested have matured; (2) when 60% of bolls are open; and (3) when there are no more than four nodes between the highest first position cracked boll and the highest first position harvestable

boll. The label recommends that application be made with a crop oil concentrate (1 pt/A) or non-ionic or silicone-based surfactant (1 qt/100 gal). The product may be tank-mixed with other commonly used cotton harvest aids, such as cyclanilide + ethephon, dimethipin, diuron + thidiazuron, ethephon, endothall, glyphosate, paraquat dichloride, sodium chlorate, thidiazuron, and tribufos, but the most restrictive label limitations and precautions for the products being mixed must be followed.

2.2 Structure and Nomenclature

Table 2.2 outlines the structure, nomenclature and some basic information for fluthiacet-methyl.

Table 2.2	**Fluthiacet-Methyl Nomenclature.**
Chemical structure	
Empirical Formula	$C_{15}H_{15}N_3O_3ClFS_2$
Common name	Fluthiacet-methyl
Company experimental name	CGA-248757
IUPAC name	3-[(4-chloro-2-fluoro-5-methylphenyl)imino]tetrahydro[1,3,4]thiadiazolo[3,4-a]pyridazin-1-one
CAS name	[[2-chloro-4-fluoro-5-[(tetrahydro-3-oxo-1*H*,3*H*-[1,3,4]thiadiazolo[3,4-a]pyridazin-1-ylidene)amino]phenyl]thio]acetic acid, methyl ester
CAS registry number	117337-19-6
End-use product (EP)	Appeal™ EC (0.91 lb ai/gal EC formulation; EPA Reg. No. 63588-8)
Chemical Class	Imine
Known Impurities of Concern	None

2.3 Physical and Chemical Properties

Table 2.3 outlines the physical and chemical properties of fluthiacet-methyl. Technical fluthiacet-methyl is a solid, odorless powder. Due to its solid nature and low vapor pressure, inhalation exposure is dependent on the compound becoming aerosolized when the liquid formulation is sprayed on the target crop.

Table 2.3	**Physicochemical Properties of Fluthiacet-Methyl.**	
Parameter	Value	Reference
Molecular Weight	403.9	EPA Pesticide Fact Sheet, Fluthiacet-Methyl, April 1999

Table 2.3 Physicochemical Properties of Fluthiacet-Methyl.		
Parameter	Value	Reference
Melting point range	105-106.5 °C, with decomposition	EPA Pesticide Fact Sheet, Fluthiacet-Methyl, April 1999
pH	6.29 at 24.3 °C (1% aqueous dispersion)	EPA Pesticide Fact Sheet, Fluthiacet-Methyl, April 1999
Density	0.43 g/cm^3 at 20 °C	EPA Pesticide Fact Sheet, Fluthiacet-Methyl, April 1999
Water solubility	0.85 µg/L at 25 °C 0.78 µg/L (pH 5 and 7) 0.22 µg/L (pH 9)	EPA Pesticide Fact Sheet, Fluthiacet-Methyl, April 1999
Solvent solubility	g/L acetone 10.1 acetonitrile 6.87 dichloromethane 53.1 ethyl acetate 7.35 n-hexane 0.0232 n-octanol 0.186 methanol 0.441 toluene 8.40	EPA Pesticide Fact Sheet, Fluthiacet-Methyl, April 1999
Vapor pressure	3.31 x 10^{-9} mm Hg at 25 °C	EPA Pesticide Fact Sheet, Fluthiacet-Methyl, April 1999
Dissociation constant, pK_a	no dissociation from pH 1 to pH 9	EPA Pesticide Fact Sheet, Fluthiacet-Methyl, April 1999
Octanol/water partition coefficient, Log(K_{OW})	log P_{ow} = 3.769 at 25 °C	EPA Pesticide Fact Sheet, Fluthiacet-Methyl, April 1999
UV/visible absorption spectrum	Not available	

3.0 Metabolism Assessment

References:
CGA-248757: Review of a Guideline Metabolism Study, MRID 438300-18, -19 and -20, Timothy McMahon, 10/18/96, D224320.

PP#7F4821; Fluthiacet-methyl (Action Herbicide, EPA Reg. No. 100-805) in/on Field Corn, Pop Corn, Sweet Corn, and Cotton. Briefing Memorandum for Metabolism Assessment Review Committee, William Wassell, 10/25/2000, D268759.

PP#7F4821; Fluthiacet-methyl in/on Field Corn, Sweet Corn, Pop Corn and Cotton. Conclusions of the 10/31/2000 Meeting of the Metabolism Assessment Review Committee, William Wassell, 2/6/01, D272221.

PP#7F4821 Fluthiacet-methyl in/on Field Corn, Sweet Corn, Pop Corn and Cotton. Evaluation of Metabolism Data, Magnitude of Residue Data, and Analytical Methodology, William Wassell, 2/20/01, D234717,D234495, D238930, D239384, D249645, D257126.

Review of New Use for Fluthiacet-methyl (Appeal EC; previously identified as CGA248757) as a defoliant in cotton, Keara Moore, 11/1/05, D304797.

3.1 Comparative Metabolic Profile

The rat metabolism studies indicate fluthiacet-methyl is absorbed rapidly at both low- and high-doses, and that repeated oral dosing has no effect on the extent of absorption. Excretion in males was predominantly in feces for all dose groups (67 - 87% of administered radioactivity); whereas in females excretion was approximately equal in urine and feces, (40 - 48% and 39 - 52% of administered radioactivity, respectively) across all dose groups. Presumably, the difference was due to a greater percentage of excretion in bile for males (37%) versus females (19%). The predominant fecal, urinary and biliary metabolites were CGA-300403 and CGA-330063/330064 (although for the biliary metabolites, CGA-327066 and CGA-340350 were identified at similar levels). In addition to the predominant metabolites, parent, CGA-300402, CGA-330059, CGA-330065, unknowns (U1, U3, U5), and Polar 8 were identified.

The proposed primary metabolic pathway in the rat involves isomerization of fluthiacet-methyl to form CGA-277507 and hydrolysis of the methyl ester to form free carboxylic acid compounds. Although fluthiacet-methyl and the free acid CGA-300402 are only observed in significant quantity in the feces of high dose groups, the rearranged free acid CGA-300403 is observed in almost all dose groups as a major metabolite, as a result of rapid rearrangement/hydrolysis of fluthiacet-methyl. CGA-300403 acts as a pivotal structure from which other important metabolites are derived, such as CGA-330063/330064 which result from hydroxylation at the 6/7 positions of the pyridazine ring. Furthermore, oxidation of the sulfur in the thioacetate group of CGA-300403 yields the sulfoxide, CGA-330059 and desulfuration of the thiocarbonyl in CGA-300403 results in the formation of CGA-327066 and related metabolites (the proposed structure of Polar 8 is most likely related to this process). Multiple oxidation products identified in the rat metabolism study include CGA-327067 and CGA-340350. The study indicated that the bridge between the pyridazine and phenyl rings is stable metabolically and chemically (no cleaved products were identified).

The livestock metabolism studies are different than the rat metabolism study, in that fluthiacet-methyl was poorly absorbed by both lactating goats and laying hens; however, what does get metabolized in goats and hens, appears to follow a generally similar pathway as that in the rat. In lactating goats approximately 63 to 77% of the administered radioactivity was contained in the feces and urine, while less than 0.15% was found in the tissues, and less than 0.01% was in the milk. The majority of the residue in urine consisted of CGA-300403 (free acid rearranged parent, ~ 70% TRR) and a mixture of CGA-330063 and CGA-330064 (~28% TRR). The majority of the residue in feces consisted of fluthiacet-methyl (~ 54% TRR), CGA-300402 (~15% TRR), CGA-300403 (~25% TRR), and a mixture of CGA-330063 and CGA-330064 (~2% TRR). The primary metabolic pathway for fluthiacet-methyl in lactating goats appears to involve rearrangement and ester hydrolysis to the free acid CGA-300403. A secondary pathway involves oxidation at the 6/7 positions of the pyridazine ring to form CGA-330063/-330064 (hydroxylated equivalents of CGA-300403). A minor oxidative pathway involves the desulfurization of CGA-300403 to form CGA-327066. The parent compound (CGA-248757) and the free acid of parent (CGA-300402) were not detected in tissues, milk, bile, or urine. And as with the rat, evidence of bridge cleaved metabolites was not found.

As with lactating goats, the data show that laying hens orally dosed with fluthiacet-methyl absorb little of it. A large portion of the residue is eliminated as unmetabolized parent (~52% TRR). A large majority of the administered dose was contained in the excreta, and in addition to fluthiacet-

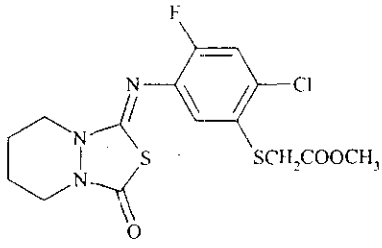
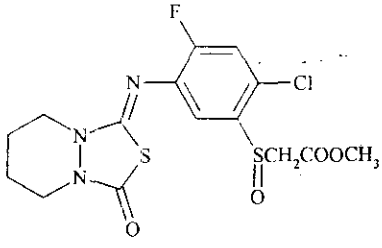
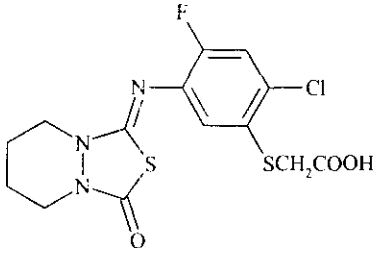
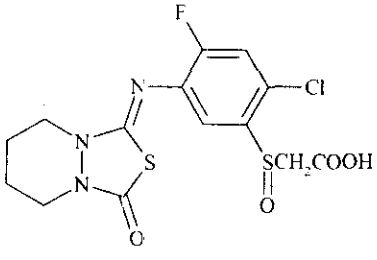
methyl, CGA-300403 (~39% TRR) and small amounts of CGA-300402, CGA-327066, CGA-33059 and an unidentified polar metabolite were also found. As with lactating goats, the primary metabolic pathway for CGA-248757 in laying hens appears to involve rearrangement and hydrolysis to the free acid CGA-300403. And a minor oxidative pathway involves the desulfurization of the side chain to form CGA-330059 or desulfurization to form CGA-327066. The presence of the metabolites CGA-300403 and CGA-327066 was based upon the identification of their methyl esters CGA-277507 and CGA-330062, respectively, following hydrolysis and esterification of the aqueous soluble fractions in liver and whole egg. And as with the rat and lactating goat, evidence of bridge cleaved metabolites was not found.

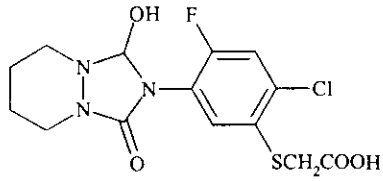
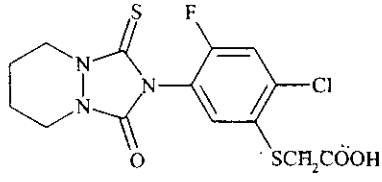
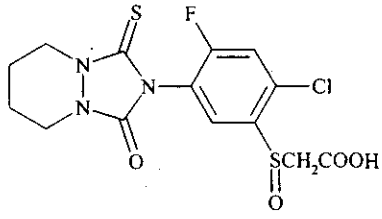
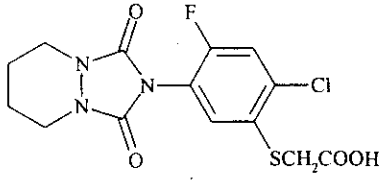
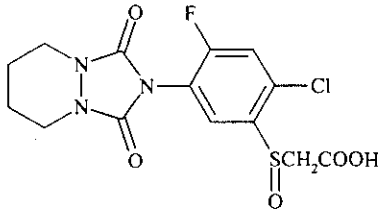
The metabolism of fluthiacet-methyl in rats, lactating goats and laying hens appears to proceed in a similar fashion with some exceptions. Metabolites (CGA-330063/-330064, CGA-330056, and CGA-330060) resulting from the oxidation of the pyridazine ring of the test substance were not detected in laying hens, whereas they were in lactating goats; these metabolites were present in the tissues, milk, urine, and feces of lactating goats dosed with fluthiacet-methyl. Furthermore, metabolite CGA-330059, resulting from oxidation of CGA-300403, was identified in rats and laying hens, but not in lactating goats. Additionally, CGA-300403 underwent oxidation/hydrolysis to form CGA-330065 and Polar 8 in rats, but not in lactating goats or laying hens; and likewise, the hydroxylation of CGA-327066 to CGA-340350 was only observed in the rat. Finally, in lactating goats only, the hydroxylation and oxidation of CGA-277507 resulted in CGA-330056/330060 and CGA-330062, respectively.

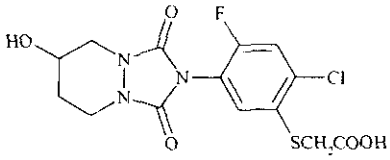
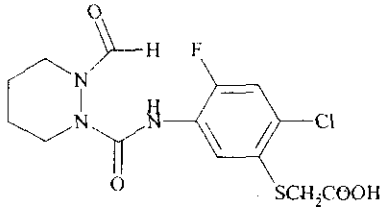
Metabolism in plants works a little differently; whereas CGA-300403 featured prominently in animal metabolic pathways, CGA-300402 features prominently in the plant metabolic pathways. Based on the metabolism studies with field corn, cotton, and soybean, it appears that fluthiacet-methyl is metabolized rapidly, primarily via hydrolysis of the methyl ester to produce the free acid CGA-300402, which then undergoes oxidization to produce the free acid sulfoxide, CGA-300404, or isomerization via rearrangement of the thiadiazole ring to produce CGA-300403. CGA-300403 may undergo further oxidation to form CGA-327066 or CGA-330059; CGA-327066 may undergo (i) sulfoxidation to form CGA-327067, (ii) ring opening to form CGA-330065, or (iii) hydroxylation of the pyridazine ring to form CGA-340350. In a minor pathway, fluthiacet-methyl may undergo sulfoxidation to produce CGA-330057. Based on the corn metabolism study, it appears that fluthiacet-methyl intermediates may also undergo further oxidation/conjugation to produce complex aqueous-soluble components and sugar and amino acid conjugates. Based on studies in corn, cotton, and soybeans, there is no evidence that bridge cleavage occurs in the metabolic pathway of fluthiacet-methyl - which is the same as in the animal metabolism studies.

The metabolites in the rat metabolism study correspond well with the metabolites identified in plant and livestock metabolism studies. Of note, CGA-330057, CGA-300404, and CGA-327067 were identified in plant metabolism, but not rat metabolism studies (William Wassell, 2/6/01, D272221; William Wassell, 2/20/01, D234717; Michael Doherty, 11/22/05, D304795).

Table 3.1 Structure of Fluthiacet-methyl and Metabolites*

Common Name/Chemical Code Chemical Name	Structure	Substrate
Fluthiacet-methyl/CGA-248757 acetic acid, [[2-chloro-4-fluoro-5-[(tetrahydro-3-oxo-1*H*,3*H*-[1,3,4]thiadiazolo[3,4-α]pyridazin-1-ylidene)amino]phenyl]thio]-methyl ester		Corn forage, silage, and fodder Cotton gin byproduct Rat
CGA-330057		Corn forage, silage, and fodder
CGA-300402		Corn forage, silage, and fodder Cotton gin byproduct, cottonseed Rat
CGA-300404		Corn forage, silage, and fodder Cotton gin byproduct, cottonseed

Common Name/Chemical Code Chemical Name	Structure	Substrate
Metabolite B1/Polar 8		Corn silage and fodder Rat
CGA-300403		Cotton gin byproduct, cottonseed Rat
CGA-330059		Cotton gin byproduct, cottonseed Rat
CGA-327066		Cotton gin byproduct, cottonseed Rat
CGA-327067		Cotton gin byproduct

Common Name/Chemical Code Chemical Name	Structure	Substrate
CGA-340350		Cotton gin byproduct Rat
CGA-330065		Cotton gin byproduct, cottonseed Rat

*The structures of some metabolites and degradates are not available, and therefore not included in this table (CGA-330063/-330064, U1, U3, U5, and A-CFPSA).

3.2 Environmental Degradation

Fluthiacet-methyl is non-persistent in aerobic and anaerobic environments, and is mobile to very mobile in a range of soils (*i.e.*, could potentially reach surface water and/or groundwater). However, the environmental fate of fluthiacet-methyl is complicated by multiple degradates, several of which are expected to be herbicidally active and others which are not, but have the potential to be toxic to humans and other animals. Although the group of herbicidally active degradates are moderately persistent and more mobile than the parent, only one is included in the drinking water assessment (which considers major degradates, *i.e.*, degradates which comprise greater than or equal to 10% of the total radioactive residues in the environmental fate studies). For the drinking water assessment, in addition to fluthiacet-methyl (which is mobile to very mobile, but non-persistent), CGA-300402 (also herbicidally active), CGA-300403, CGA-327066, CGA-327067, and A-CFPSA were considered, and as a group, these five major degradates are persistent and very mobile. Effective half-lives in aerobic and anaerobic soil conditions were calculated to be 305 and 26 days, respectively. Given the stability of these compounds to hydrolysis and their mobility, these degradates have a high potential for movement via runoff water and leaching, a potential that lasts several days to weeks and possibly much longer. (Keara Moore, 11/1/05, D304797).

3.3 Summary of Residues for Tolerance Expression and Risk Assessment

3.3.1 Tabular Summary

Table 3.3.1 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	Corn and Soybeans	fluthiacet-methyl	fluthiacet-methyl
	Cotton	fluthiacet-methyl and CGA-300402	fluthiacet-methyl and CGA-300402
	Rotational Crop	No uptake of residues	Tolerances not required
Livestock	Ruminant	fluthiacet-methyl and CGA-300403*	fluthiacet-methyl and CGA-300403*
	Poultry	fluthiacet-methyl and CGA-300403*	fluthiacet-methyl and CGA-300403*
Drinking Water		fluthiacet-methyl, CGA-300402, CGA-300403, CGA-327066, CGA-327067, A-CFSPA	Not Applicable

*Although there were residues of concern identified in the livestock metabolism studies for both risk assessment and tolerance expression purposes, as per 180.6(a)(3), it was determined that there is no reasonable expectation of finite residues in livestock commodities. Therefore, dietary exposures to fluthiacet-methyl and CGA-300403 from livestock commodities are not included in the dietary exposure assessment, nor will there be livestock commodity tolerance published in the CFR at this time.

3.3.2 Rationale for Inclusion of Metabolites and Degradates

The residues included in the risk assessment and tolerance expression for corn and soybeans were determined to be parent only because the predominant residue identified in the field corn and soybean metabolism studies was fluthiacet-methyl. All other residues identified, with the exception of CGA-300402 in some samples, were at very low levels (generally less than 0.01 ppm). And the residues of CGA-300402 that were identified at significant levels in field corn samples were collected at a zero-day pre-harvest interval (PHI). Since PHIs for corn and soybeans are significantly longer than zero days, and residues of CGA-300402 declined to insignificant levels at PHIs of 30-days or longer, the MARC deemed it inappropriate to set tolerances and/or perform a risk assessment for residues of CGA-300402 in corn and soybeans.

The residues included in the risk assessment and tolerance expression for cotton were determined to be fluthiacet-methyl and metabolite CGA-300402, because these compounds were the predominant residues identified in the cotton metabolism study (cotton gin byproduct samples), and data suggest detectable residues (>0.01 ppm) of CGA-300402 may occur in treated cotton commodities. Since there is no evidence that CGA-300402 is significantly less toxic than the parent compound, it is presumed that the metabolite is of comparable toxicity to the parent compound.

In the livestock metabolism studies, HED determined that the residues of concern for tolerance setting and risk assessment purposes for secondary residues in livestock are fluthiacet-methyl and

its metabolite designated as CGA-300403. This decision was made because residues of CGA-300403 were the predominant residue identified in the poultry and ruminant metabolism studies. The analytical method developed for the analysis of livestock tissues determines residues of fluthiacet-methyl and CGA-300403. In this method residues of the parent compound are converted to CGA-300403 and determined as residues CGA-300403. There is no evidence that CGA-300403 is significantly less toxic than the parent compound. Thus, it is presumed that the metabolite is of comparable toxicity to the parent compound. Although there were residues of concern identified in the livestock metabolism studies for both risk assessment and tolerance expression, as per 180.6(a)(3), it was determined that there is no reasonable expectation of finite residues in livestock commodities. Therefore, dietary exposures from livestock commodities are not included in the dietary exposure assessment, nor will there be livestock commodity tolerance published in the CFR at this time.

The MARC concluded that it is not necessary to determine the residues of concern in rotational crops because all samples from the confined rotational crop study exhibited total radioactive residue (TRR) levels less than 0.01 ppm. Thus, there is no concern for the uptake of residues into rotational crops following applications of fluthiacet-methyl to corn, soybeans, and cotton at the proposed use rates. If additional uses are proposed with higher application rates, an additional confined rotational crop study may be required at those higher application rates (W. Wassell, 2/6/01, D272221).

The residues of concern for the risk assessments and tolerance expressions in plant and livestock matrices were determined to be fluthiacet-methyl alone, or fluthiacet-methyl with either CGA-300402 or CGA-300403. Since these three species were identified in the rat metabolism study (along with a variety of other metabolites), the fluthiacet-methyl toxicology database has adequately accounted for exposure to the determined residues of concern. Although the water matrix includes CGA-327067 and A-CFSPA, which were not quantified in the rat metabolism study, as discussed below, these degradates are considered to have comparable toxicity to fluthiacet-methyl (William Wassell, 2/6/01, D272221; William Wassell, 2/20/01, D234717; Michael Doherty, 11/22/05, D304795).

The MARC determined that for risk assessment purposes the residues of concern in water are residues that comprise greater than or equal to 10% of the total radioactive residues in the environmental fate studies. These residues include fluthiacet-methyl, CGA-300402, CGA-300403, CGA-327066, CGA-327067 and A-CFSPA. In various environmental fate studies, the parent compound is readily degraded to produce many metabolites. Numerous metabolites of fluthiacet-methyl (over 30) were identified in these studies. Some of the metabolites may be more mobile than the parent compound. There is no evidence that identified degradates of the environmental fate studies are significantly less toxic than the parent compound. Thus, it is presumed that these metabolites are of comparable toxicity to the parent compound. Metabolite residues are included in the surface water and groundwater modeling so that exposure to residues in water are not underestimated as could be the case if only parent residues were included in the modeling (W. Wassell, 2/6/01, D272221).

3.4 Analytical Methods

Cotton Commodity Method
Enforcement method: K-I Chemical U.S.A., Inc. has proposed a gas chromatography/mass spectrometry method which uses negative ion chemical ionization (GC/NCI-MS), Meth-150 Revision #2, for the enforcement of tolerances for residues of fluthiacet-methyl and its metabolite CGA-300402 in cotton commodities. The GC/NCI-MS method, entitled "Determination of Fluthiacet-methyl and CGA-300402 in Cotton and Cotton Byproducts," was used to determine residues of fluthiacet-methyl and CGA-300402 in/on samples of cotton seed, gin byproducts, and processed commodities (meal, hulls, and refined oil) from the storage stability, crop field trial, and processing studies associated with DP Barcode D304795.

Method validation data for GC/NCI-MS method Meth-150 Revision #2 demonstrated adequate method recoveries of fluthiacet-methyl and CGA-300402 at 0.01 ppm (LOQ), 0.10 ppm and 1.0 ppm from cotton seed, gin byproducts, and refined oil. Adequate independent laboratory validation data have been submitted for the method using samples of cotton seed, gin byproducts, and refined oil. RAB3 has determined that radiovalidation data are not required for the method because the extraction procedures are similar to those used in the cotton metabolism study.

Conclusions: The plant commodity residue analytical method data are adequate to satisfy data requirements. In the previous review the petitioner was required to submit an enforcement analytical method for the determination of residues of CGA-300402 in/on cotton commodities and have the method validated by an independent laboratory. The petitioner has submitted an adequate enforcement method for the determination of residues of fluthiacet-methyl and CGA-300402 in/on cotton commodities. The proposed enforcement method will be forwarded to ACB/BEAD for petition method validation. Pending ACB/BEAD validation of the method, the requirements of Conclusion 8c of the previous review have been fulfilled (William Wassell, 2/20/01, D234717).

Livestock commodity method
No residue analytical methods are required for livestock commodities since tolerances for secondary residues in livestock tissues are not required as a result of the proposed uses of fluthiacet-methyl on cotton and the established uses on corn and soybeans.

Multiresidue Methods
Kumiai Chemical Industry Company, Ltd., on behalf of K-I Chemical, U.S.A., Inc., has submitted multiresidue method data for CGA-300402, a metabolite of fluthiacet-methyl. The test substance was analyzed according to the FDA Multi-Residue Method Test guidelines in PAM Vol. I (dated 1/94). CGA-300402 was tested through Protocols A, B, and C.

Testing under Protocol A was terminated because CGA-300402 was not found to be naturally fluorescent. Because CGA-300402 is an acid, it was evaluated under Protocol B. Protocol C testing of methylated CGA-300402 (fluthiacet-methyl) yielded peaks within acceptable relative retention time limits in two modules, however, sensitivity was not adequate for quantitation. Based on the results for Protocol C, further testing under Protocols B, D, E, and F was not required for CGA-300402.

Conclusions: In the previous review, the petitioner was required to submit multiresidue method data for metabolite CGA-300402; the petitioner has now satisfied the requirements of Conclusion 10b the previous review. Based on the results of the testing, the multiresidue methods are not appropriate for determining residues of fluthiacet-methyl or CGA-300402.

4.0 Hazard Characterization/Assessment

References:

Fluthiacet-methyl (CGA-248-757; Action™) - Report of the Hazard Identification Assessment Review Committee, Alan C. Levy, 6/16/98, HED Doc. No. 012644

Evaluation of the Carcinogenic Potential of Fluthiacet-methyl, CARC Final Report, A. Levy and J. Rowland, 11/20/98, HED Doc. No. 012784.

Fluthiacet-methyl (CGA-248757; Action™) - REVISED Report of the FQPA Safety Factor Committee, 6/11/98, TXR No.012643.

4.1 Hazard Characterization

The studies itemized in Tables 4.1a and 4.1b were considered in determining the hazard posed by fluthiacet-methyl. As shown in Table 4.1a, technical grade fluthiacet-methyl has low acute oral, dermal and inhalation toxicity. It is non-irritating to skin and minimally irritating to eyes, and is not a skin sensitizer.

Table 4.1a Summary of Acute Toxicity for Technical Fluthiacet-methyl

Guideline	Study	Species	Results	Tox Cat	MRID No.
81-1	Acute oral LD50	rat	LD50 males & females >5,000 mg/kg	4	43348411
81-2	Acute dermal LD50	rabbit	LD50 males & females >2,000 mg/kg	3	43348412
81-3	Acute inhalation LC50	rat	LC50 males & females >5,048 ± 225 mg/m^3 (>5.0 mg/L)	4	43348413
81-4	Primary eye irritation	rabbit	minimum eye irritant	3	43348414
81-5	Primary dermal irritation	rabbit	no dermal irritation	4	43348415
81-6	Dermal sensitization	guinea pig	not a dermal sensitizer	N/A	43348416

As shown in Table 4.1b, subchronic studies in rats, mice and dogs demonstrated that the primary effects of fluthiacet-methyl were on hematology parameters and the liver. Similarly, in the chronic studies, the effects primarily targeted the erythropoietic system and the liver. Additionally, in a combined chronic/carcinogenicity study in rats, there was an increase in the trend toward pancreatic exocrine adenomas and pancreatic islet cell adenomas in males, as well as liver and uterine toxicity, and slight microcytic anemia in females. Furthermore, in a carcinogenicity study in mice, there were indications of an increase in the number of animals with hepatocellular adenomas, carcinomas and/or combined adenomas/carcinomas. The results of the two-generation reproduction and developmental toxicity studies indicated that fluthiacet-methyl is not a significant developmental or reproductive toxicant, and fluthiacet-methyl was not identified as an acute neurotoxicant.

Table 4.1b Toxicity Profile Table for Fluthiacet-methyl: Table of Subchronic, Chronic, and Other Toxicitiy

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100a 90-Day oral toxicity rodents (rats)	43348423 (1993)/ acceptable/guideline mg/kg/day: males = 0, 0.60, 6.19, 216, 427 and 1,224; females = 0, 0.69, 6.80, 249, 490 and 1,424	NOAEL = **6.19** mg/kg/day in males 6.80 mg/kg/day in females LOAEL = **216** mg/kg/day in males 249 mg/kg/day in females Based on **decreased body weight gains as well as effects on hematology, clinical chemistry, urinalysis parameters, liver weights and microscopic pathology in rats.**
870.3100b 90-Day oral toxicity rodents (mice)	43357804 (1992)/ acceptable/ guideline mg/kg/day: males = 0, 0.13, 1.3, 66 and 655; females = 0, 0.17, 1.6, 83 and 782	NOAEL = **1.3** mg/kg/day in males 1.6 mg/kg/day in females LOAEL = **66** mg/kg/day in males 83 mg/kg/day in females Based on **effects on the erythropoietic system and liver in mice.** Effects on the erythropoietic system (decrease in hemoglogin, hematocrit, mean corpuscular volume and mean corpuscular hemoglobin; elevation of platelet counts; decreases in bone marrow smear myeloid:erythroid ratio and Erythrocyte Maturation Index; increases ingranulopoiesis in bone marroiw; extramedullary hematopoiesis) and the liver (increase in absolute and relative liver weights, sorbitol dehydrogenase, alanine aminotransferase, aspartate aminotransferase, 5'nucleotidase, bile acids, fatty changes, chronic inflammation, karyomegaly, single cell necrosis, ceroid/lipofuscin pigmentation).
870.3150 6-Week oral toxicity (nonrodents-dogs)	43348427 (1993)/ acceptable/guideline mg/kg/day: males = 0, 18.1, 75.1, 236, 709 and 1,943; females = 0, 19.6, 77.7, 232, 766 and 2,126	NOAEL = **236** mg/kg/day in males 77.7 mg/kg/day in females LOAEL = **709** mg/kg/day in males 232 mg/kg/day in females Based on **decreased body weight gain.**
870.3200 28-Day dermal toxicity (rats)	43348424 (1993)/ acceptable/guideline 0, 10, 100 or 1,000 mg/kg/day	NOAEL = 1,000 mg/kg/day, the highest dose tested (HDT)
870.3700a Prenatal developmental toxicity (rats)	43348426 (1993)/ acceptable/guideline 0, 5, 300 or 1,000 mg/kg/day	Maternal NOAEL = **1,000** mg/kg/day, HDT Developmental NOAEL = **1,000** mg/kg/day
870.3700b Prenatal developmental toxicity (rabbits)	43348425 (1993)/ acceptable/guideline 0, 5, 300 and 1,000 mg/kg/day	Maternal NOAEL = **1,000** mg/kg/day, HDT Developmental LOAEL of **300** mg/kg/day Based on **slight non-significant increased incidence of irregularly shaped sternebrae attributed to a delay in fetal development.**

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3800 Reproduction and fertility effects (rats)	43830016 (1994)/ acceptable/guideline mg/kg/day: males = 0, 1.59, 31.8 or 313 for the P generation and 0, 1.73, 35.2 or 361 for the F1 generation; females = 0, 1.78, 36.2 or 369 for the P generation and 0, 1.86, 37.1 or 388 for the F1 generation	Parental/Systemic NOAEL = **1.59** mg/kg/day in males 1.73 mg/kg/day in females LOAEL = **31.8** mg/kg/day in males 35.2 mg/kg/day in females Based on **reduction in male body weights/gains and hepatic pathology**. Reproductive NOAEL = **31.8** mg/kg/day in males 37.1 mg/kg/day in females LOAEL =**313** mg/kg/day in males 388 mg/kg/day Based on **decreases in mean litter body weights.**
870.4100b Chronic toxicity (dogs)	43830014 (1994)/ acceptable/guideline mg/kg/day: males = 0, 0.351, 4.19, 57.6 or 582; females = 0, 0.313, 5.00, 30.3 or 145	NOAEL = **57.6** mg/kg/day in males 30.3 mg/kg/day in females LOAEL = **582** mg/kg/day in males 145 mg/kg/day in females Based on effects observed in the **erythropoietic system and liver**. Effects noted: a decrease in mean corpuscular volume in both sexes as well as a decrease in mean corpuscular hemoglobin in males only; effects on the liver (both sexes) were an increase and/or severity of hepatocyte degeneration, leukocytosis, Kupffer cell pigmentation and intracytoplasmic pigmentation.
870.4300 Combined Chronic/carcinogenicity (rats)	43830017 (1995)/ acceptable/guideline mg/kg/day: males = 0, 0.2, 2.1, 130 or 219; females = 0, 0.2, 2.5, 154 or 368	NOAEL = **2.1** mg/kg/day in males 2.5 mg/kg/day in females LOAEL = **130** mg/kg/day in males 154 mg/kg/day in females In **males** there were **decreased body weight, liver toxicity, pancreatic toxicity and microcytic anemia**. In **females** there were **liver toxicity, uterine toxicity and slight microcytic anemia**. In **males only** at 130 and 219 mg/kg/day there was respectively, an **increase in the trend toward pancreatic exocrine adenomas and pancreatic islet cell adenomas.**
870.4200b Carcinogenicity (mice)	43830015 (1995)/ acceptable/guideline mg/kg/day: males = 0, 0.1, 1.0, 10 or 32; females = 0, 0.1, 1.2, 12 or 37	NOAEL = **0.1** mg/kg/day in males and females LOAEL = **1.0** mg/kg/day in males 1.2 mg/kg/day in females Based on **non-neoplastic liver findings**. In males, and possibly females, at 10 mg/kg/day for males and 12 mg/kg/day for females; and at 32 gm/kg/day for males and 37 mg/kg/day for females, there was an **increase in the number of mice with hepatocellular adenomas, carcinomos and or adenomas/carcinomas**.
870.5100 Bacterial gene mutation 870.5300 *In vitro* mammalian cell gene mutation	43348429 (1990)/ acceptable/guideline 43348433 (1992)/ acceptable/guideline 43348435 (1993)/ acceptable/guideline	Flutiacet-methyl was negative for mutagenic/genotoxic effects in bacterial or cultured mammalian cells and did not cause DNA damage in bacterial or primary rat hepatocytes.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.5375 *In vitro* Cytogenetics	43348432 (1993)/ acceptable/guideline 43348434 (1993)/ acceptable/guideline 43348431 (1991)/ acceptable/guideline	*In vitro* cytogenetic assays performed with two different mammalian cell lines demonstrated that fluthiacet-methyl is clastogenic both in the presence and absence of S9 activation.
870.5395 *In vivo* cytogenetic (micronucleus) test in mice	43348436 (1991)/ acceptable/guideline	Flutiacet-methyl was negative for micronuclei induction in mouse bone marrow, **a significant increase in micronuclei was seen in stimulated rat liver cells following *in vivo* exposure.**
Other genotoxicity	43348428 (1990)/ acceptable/guideline 43348430 (1993)/ acceptable/guideline	Flutiacet-methyl was negative for *in vitro* induction of Unscheduled DNA synthesis, and not associated with lethal damage in *E. coli*.
870.6200a Acute neurotoxicity screening battery (rats)	43830012 (1995)/ acceptable/guideline 0, 10, 1,000 or 2,000 mg/kg	NOAEL = **2,000** mg/kg/day, with no effects at HDT.
870.6200b Subchronic neurotoxicity screening battery (rats)	43830013 (1995)/ acceptable/guideline mg/kg/day: males = 0, 0.576, 556 or 1,128; females = 0, 0.562, 668 or 1,354	NOAEL = **0.576** mg/kg/day in males 1,345 mg/kg/day in females (HDT) LOAEL = **556** mg/kg/day in males Based on **decreased body weight and food consumption**.
870.7485 Metabolism and pharmacokinetics (rats)	43830018-20 (1995)/ acceptable/guideline 1.0 mg/kg or 200 mg/kg	Fluthiacet-methyl was absorbed rapidly at both low and high dosages in both male and female rats. Repeated oral dosing had no effect on extent of absorption. Tissue levels of radio active fluthiacet-methyl in single and repeated low dose groups did not exceed 0.018 ppm in any tissue. At the single high dose, female rats showed higher levels of radioactivity in tissues than males except for muscle, brain, fat and plasma. Excretion in males was predominantly in feces for all dose groups, with between 67 to 87% of administered radioactivity excreted by this route. In females, the percentage of administered radioactivity in urine across all dose groups 40 to 48% was approximately equivalent to the percent excreted in feces, 39 to 52%. The greater fecal excretion in males was based on a greater percentage excretion in bile for males, 37% vs. females 19%.
870.7600 Dermal penetration	Not Available	No dermal penetration studies were submitted.
Special studies	Not Available	There were no required special studies.

NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level

***Note:* Electronic versions are not available for all studies.**

4.2 FQPA Considerations

4.2.1 Neurotoxicity Data

Acceptable acute and subchronic neurotoxicity studies in rats have been submitted to the Agency. Treatment-related neurotoxic effects were not observed in either study, nor in other studies with fluthiacet-methyl. There are no data gaps for the assessment of the neurotoxic potential of fluthiacet-methyl.

4.2.2 Determination of Susceptibility

The data provided no indication of increased susceptibility in young rats following *in utero* exposure; no maternal or developmental toxicity was seen at the Limit-Dose (1,000 mg/kg/day). No increased susceptibility was seen in the two-generation reproduction study in rats where the effects in the offspring were observed only at a higher dose than that which caused parental toxicity. In the prenatal developmental study with rabbits, *in utero* exposure did not result in maternal toxicity at 1,000 mg/kg/day. Developmental toxicity at 300 mg/kg/day, however, was seen at this dose as an increase in irregular sternebrae (an effect attributed to a delay in fetal development, a variation which is reversible). The occurrence of developmental toxicity at a dose at which no maternal toxicity was noted indicates an apparent susceptibility. The HIARC, however, determined that the apparent susceptibility is not convincing for the following reasons: 1) the increased incidence of irregular sternebrae was not statistically significant when compared to concurrent controls; 2) the increase occurred primarily at the Limit-Dose (1,000 mg/kg/day); 3) it was the only anomaly observed in the study (i.e., a single variation); 4) the dose response was not strong since there was only a small increase in the litter incidences between the low-dose (5 mg/kg/day) and the high-dose (1,000 mg/kg/day), with the mid- and high-dose groups having 8 litters with this variation; and 5) this endpoint is considered appropriate to establish a LOAEL, but not appropriate for risk assessments. Based on these factors, the HIARC concluded that there is no increased susceptibility in the rabbit study.

4.2.3 Recommendation for a Developmental Neurotoxicity Study

There was no evidence in the database that would support a requirement for a developmental neurotoxicity study.

4.2.4 Determination of the FQPA Factor

Based on the hazard assessment, the HIARC recommended that application of the 10x FQPA safety factor to ensure the protection of infants and children be removed based on the lack of increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure to fluthiacet-methyl.

The HED FQPA Safety Factor Committee met on April 27, 1998 to evaluate the hazard and exposure data for fluthiacet-methyl and to determine the application of the FQPA Safety Factor (as required by FQPA), to ensure the protection of infants and children from exposure to this chemical. The Committee recommended that the 10x FQPA safety factor be removed, based

upon: (1) the HIARC determination that the available hazard assessment studies indicated no increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure to fluthiacet-methyl; and, (2) exposure assessments do not indicate a concern for potential risk to infants and children, based upon: (a) the very low application rates and quick dissipation of fluthiacet-methyl; (b) the dietary exposure estimates using tolerance level residues, modified by percent crop treated information result in an overestimate of dietary exposure; (c) modeling data are used for ground and surface source drinking water exposure assessments resulting in estimates considered to be upper-bound concentrations; and (d) there are currently no registered residential uses for fluthiacet-methyl. On August 31, 2005, the RAB3 Toxicology Team reaffirmed this conclusion to be in accordance with the 2002 policy for the FQPA safety factor.

4.2.5 Data Gaps

There are no data gaps. The toxicology database is complete for a food-use chemical as defined in 40 CFR Part 158.

4.3 Hazard Identification and Toxicity Endpoint Selection

On April 23, 1998, the HED HIARC evaluated the fluthiacet-methyl toxicology database, and selected the doses and toxicological endpoints for dietary and occupational exposure risk assessments. Additionally, on August 31, 2005, the RAB3 Toxicology Team met (*ad hoc* meeting) to re-examine the appropriateness of these toxicological endpoints, in light of new policy and newly proposed uses. Since the proposed new use on cotton entails spray applications by aerial and ground equipment, which can introduce aerosolization, short- and intermediate-term inhalation endpoints are now required. For exposure scenarios of short- or intermediate-term inhalation, the 90-day oral study in mice was chosen. The study chosen has a NOAEL of 1.3 mg/kg/day and a LOAEL of 66 mg/kg/day, based on the effects on the erythropoietic system (decrease in hemoglobin, hematocrit, mean corpuscular volume and mean corpuscular hemoglobin; elevation of platelet counts; decreases in bone marrow smear myeloid:erythroid ratio and Erythrocyte Maturation Index; increases in granulopoiesis in bone marrow; extramedullary hematopoiesis) and the effects on the liver (increase in absolute and relative liver weights, sorbitol dehydrogenase, alanine aminotransferase, aspartate aminotransferase, 5'nucleotidase, bile acids, fatty changes, chronic inflammation, karyomegaly, single cell necrosis, ceroid/lipofuscin pigmentation). This endpoint was chosen on the basis that (1) the study was of the appropriate length, (2) the study was conducted in the most sensitive species, and (3) the NOAEL for this study is in the range of that found for the reproduction study (Parental NOAEL = 1.59 mg/kg/day). The Agency's level of concern is set at an MOE of 100, considering a standard uncertainty factor of 100x.

The RAB3 Toxicology Team met again on September 12, 2005 to determine whether an estimated dermal absorption rate could be determined from existing fluthiacet-methyl toxicology studies, to refine the exposure assessment. The RAB3 Toxicology Team estimated a dermal absorption rate based on a comparison of the LOAEL/NOAELs established from similar endpoints observed in an oral reproductive study and a 21-day dermal toxicity study in the same species (rats). In the oral reproductive toxicity study in rats, the parental NOAEL of 31.8 mg/kg/day and the LOAEL of 313 mg/kg/day was based on decreased body weight/weight gain and hepatic pathology (MRID

43830016). In the 21-day dermal toxicity study, the systemic toxicity NOAEL was 1000 mg/kg/day, the highest dose tested (MRID 43348424). A ratio of the LOAEL/NOAEL from the oral and dermal studies, indicated an approximate upper bound dermal absorption rate of 31.3% (*i.e.*, oral LOAEL of 313 mg/kg/day ÷ dermal NOAEL of 1000 x 100 = 31.3%). Since there was no LOAEL in the dermal study, and therefore this calculation was based on the dermal study's NOAEL (highest dose tested), this dermal absorption rate is considered conservative.

In addition, the Cancer Assessment Review Committee (CARC) met on October 14, 1998 to evaluate the carcinogenic potential of fluthiacet-methyl. The CARC evaluated a combined chronic toxicity/carcinogenicity study in Sprague-Dawley rats and a carcinogenicity study in CD-1 mice. Evidence for carcinogenicity was demonstrated by the presence of pancreatic tumors (exocrine adenomas, islet cell adenomas and combined islet cell adenomas + carcinomas) in male rats and liver tumors (adenomas and combined adenomas + carcinomas) in male and female mice. There was no evidence of carcinogenicity in female rats. In accordance with the EPA *Proposed Guidelines for Carcinogen Risk Assessment* (April 10, 1996), the CARC classified the chemical as "likely to be a human carcinogen" (and as a B2 Carcinogen - probable human carcinogen - according to the 1986 Guidelines). The Committee recommended a linear low-dose approach (Q_1*) for human characterization and determined that extrapolation should be based on the combined hepatocellular tumors (adenomas and carcinomas) in male mice. In a memorandum (October 21, 1998, L. Brunsman to A. Levy), the unit risk, Q_1* $(mg/kg/day)^{-1}$, based upon male mouse combined (adenomas and/or carcinomas) liver tumor rates is 2.07×10^{-1} $(mg/kg/day)^{-1}$ in human equivalents (converted from animals to humans by use of the 3/4 scaling factor [Tox Risk program, Version 3.5, K. Crump, 1994; Memorandum: Deriving Q_1*s Using the Unified Interspecies Scaling Factor, P.A. Fenner-Crisp, Director, HED, 7/1/94]).

A summary of the toxicologic endpoints of fluthiacet-methyl are shown in Table 4.3 below.

Table 4.3. Summary of Toxicological Doses and Endpoints for Chemical for Use in Human Risk Assessments

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	None	No appropriate endpoint attributable to a single dose (exposure) was identified in oral toxicity studies. Therefore, an acute RfD was not established.	None
Chronic Dietary General Population	NOAEL = 0.1 mg/kg/day	Non-neoplastic liver findings (increase in absolute and relative liver weights, fatty changes, chronic inflammation, karyomegaly, single cell necrosis and ceroid/lipofuscin pigmentation).	18-month carcinogenicity in the mouse
	UF = 100	**Chronic RfD = 0.001 mg/kg/day**	
Short- & Intermediate-Term Dermal	None	No dermal or systemic toxicity was seen at the Limit-Dose following repeated dermal applications to rats.	28-day dermal in the rat

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Long-Term Dermal	NOAEL = 0.1 mg/kg/day; 31% dermal absorption factor	Non-neoplastic liver findings (increase in absolute and relative liver weights, fatty changes, chronic inflammation, karyomegaly, single cell necrosis and ceroid/lipofuscin pigmentation).	18-month carcinogenicity in the mouse
Short- & Intermediate-Term Inhalation	NOAEL = 1.3 mg/kg/day LOC = 100	LOAEL 66 mg/kg/day, based on the effects on the erythropoietic system (decrease in hemoglobin, hematocrit, mean corpuscular volume and mean corpuscular hemoglobin; elevation of platelet counts; decreases in bone marrow smear myeloid:erythroid ratio and Erythrocyte Maturation Index; increases in granulopoiesis in bone marrow; extramedullary hematopoiesis) and the effects on the liver (increase in absolute and relative liver weights, sorbitol dehydrogenase, alanine aminotransferase, aspartate aminotransferase, 5'nucleotidase, bile acids, fatty changes, chronic inflammation, karyomegaly, single cell necrosis, ceroid/lipofuscin pigmentation).	90-day oral study in mice
Cancer (Chronic)	**$Q_1^* = 0.207$ $(mg/kg/day)^{-1}$** (In human equivalents)	The CARC recommended a linear low-dose approach (Q_1^*) for human risk characterization and determined that extrapolation should be based on the combined hepatocellular tumors (adenomas and carcinomas) in male mice.	78-week carcinogenicity in the mouse

UF = uncertainty factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, RfD = reference dose, MOE = margin of exposure, LOC = level of concern

4.4 Endocrine Disruption

EPA is required under the 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 toxicity studies on fluthiacet-methyl, there was no estrogen, androgen, and/or thyroid mediated toxicity. When additional appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, fluthiacet-methyl may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

5.0 Exposure Characterization/Assessment

References:
Fluthiacet-methyl Chronic and Cancer Dietary Exposure Assessment for the Section 3 Registration Action of Fluthiacet-methyl on Cotton, Sarah Winfield, 12/5/05, D323703.

Usage Report in Support of Registration for the Defoliant Fluthiacet-Methyl (PC 108803) on Cotton. Alan Halvorson, 11/4/05, D323281.

PP#7F821 Fluthiacet-methyl (CGA-248757; Action™) on Sweet Corn, Field Corn and Pop Corn Human Health Risk Assessment, 9/4/2001, W. Wassell, D277296

5.1 Dietary (Food and Drinking Water) Exposure/Risk Pathway

5.1.1 Residue Profile

As mentioned previously, fluthiacet-methyl is currently registered for use on soybeans and corn, and its use on cotton is pending. The residue of concern in/on corn and soybean commodities for tolerance setting and risk assessment purposes is the parent compound only; whereas for cotton, both the parent and its acid metabolite CGA-300402 are considered residues of concern. The residues of concern for risk assessment purposes in water include fluthiacet-methyl, and the five major degradates CGA-300402, CGA-300403, CGA-327066, CGA-327067 and A-CFSPA (W. Wassell, 2/6/2001, D272221).

Permanent tolerances for plant commodities that result in dietary exposure are established under §180.551(a) for the residues of fluthiacet-methyl in/on: corn, field, grain at 0.010 ppm; corn, pop, grain at 0.010 ppm; corn, sweet, kernel plus cob with husks removed at 0.010 ppm; and soybean, seed at 0.010 ppm. K-I Chemical U.S.A., Inc. has submitted data pertaining to residue analytical methods, multiresidue methods, storage stability, crop field trials, and processed commodities to support use of the herbicide fluthiacet-methyl as a defoliant and harvest aid for cotton. The data were submitted to satisfy the requirements of an Agency review of PP#7F4821 (W. Wassell, 9/4/2001, D277296). The petitioner also submitted a revised Section F, proposing a tolerance for residues of fluthiacet-methyl and its acid metabolite CGA-300402 in/on cotton gin byproducts at 0.500 ppm, which HED determined was too high, and should be revised to 0.20 ppm. The petitioner did not proposed a tolerance for residues in/on cotton seed; however, HED has determined that a tolerance for the combined residues of fluthiacet-methyl and its acid metabolite CGA-300402 at 0.020 ppm in/on cotton, undelinted seed is appropriate. The available processing data in cotton processed commodities indicate that tolerances are not required for residues in/on cotton processed commodities.

The assumptions of the dietary exposure analyses were tolerance level residues, modified by default processing factors and percent crop treated (PCT) data. The resulting chronic and cancer dietary assessments are classified as Tier 2 assessments and are considered to be partially refined. PCT information came from a refined usage analysis report provided by BEAD based on data through 2004 (Alan Halvorson, 11/4/05, D323281). Refined current PCT estimates for field corn, sweet corn and soybeans were determined to be on average < 1%, and at a maximum 1%. Projected PCT estimates for cotton were determined to be on average, 30%, and at a maximum

34%. Because the estimated average PCTs for field corn, sweet corn and soybeans were less than 1%, they were rounded up to 1% for use in the chronic and cancer dietary assessments. The estimated average PCT for cotton was used for both the chronic and cancer assessments. There were no data on pop corn, and therefore 100% crop treated defaults were used. Default DEEM 7.81 processing factors were applied to corn, field, syrup and corn, field, syrup-babyfood.

Since HED concluded that residues of fluthiacet-methyl and its metabolite CGA-300403 (although identified) are not reasonably expected to accumulate in livestock tissues, livestock commodities need not be factored into the dietary risk assessment. (M. Doherty, 11/22/2005, D304795).

The drinking water values used in the dietary risk assessment were provided by the Environmental Fate and Effects Division (EFED) (Keara Moore, 11/1/05, D304797). Surface water Estimated Drinking Water Concentrations (EDWCs) of fluthiacet-methyl were made using PRZM for the field runoff processes and EXAMS for the water body processes, modeling the combined concentrations of six chemical species (fluthiacet-methyl and the five major degradates). Water-borne residues were incorporated in the DEEM-FCID™ using the food categories "water, direct, all sources" and "water, indirect, all sources." Crop scenarios used by PRZM/EXAMS represent sites that are highly vulnerable to runoff. In this assessment, cotton scenarios in California, Mississippi, and North Carolina were modeled, and the CA modeled EDWCs (which were the highest) were used in the dietary assessment. It should be noted that these scenarios assume that irrigation is not practiced at the modeled sites, while in California, cotton crops are typically irrigated. Concentrations of fluthiacet-methyl from irrigated cotton fields can be expected to be lower than those from non-irrigated fields, and therefore, the EDWCs used in the dietary assessment are considered highly conservative. A summary of the EDWCs are presented in Table 5.1. The highest chronic and cancer EDWCs were employed in the dietary assessment, and are bolded in Table 5.1. The groundwater acute and chronic EDWC was also modeled (using SCI-GROW2), but resulted in a lower estimate (0.08 ppb) and therefore was not employed in the dietary assessment.

Table 5.1 Tier II PRZM/EXAMS Surface Water EDWCs for Fluthiacet-methyl.

Modeled Scenario	Acute, 1-in-10 yr Peak (µg/L)	Chronic, 1-in-10 yr Annual Average (µg/L)	Cancer, Average of Yearly Averages (µg/L)
CA cotton	0.23	**0.19**	**0.14**
MS cotton	0.50	0.09	0.03
NC cotton	1.0	0.15	0.07

5.1.2 Chronic and Cancer Dietary Exposure and Risk

Chronic and cancer dietary (food and drinking water) risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 2.03) which uses food consumption data from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. The analyses were performed to support the Section 3 request for use

of fluthiacet-methyl on cotton, and new tolerances in/on cotton, undelinted seed and cotton, gin byproducts.

Dietary risk assessment incorporates both exposure and toxicity of a given pesticide. For acute and chronic assessments, the risk is expressed as a percentage of a maximum acceptable dose (*i.e.*, the dose which HED has concluded will result in no unreasonable adverse health effects). This dose is referred to as the population adjusted dose (PAD). The PAD is equivalent to the Reference Dose (RfD) divided by the special FQPA Safety Factor. HED is concerned when estimated dietary risk exceeds 100% of the PAD. HED is generally concerned when estimated cancer risk exceeds one in one million (*i.e.*, the risk exceeds 1×10^{-6}).

The HED HIARC concluded that no appropriate endpoint attributable to a single dose was identified in the fluthiacet-methyl toxicology database. Therefore, an acute Reference Dose (RfD) was not established and an acute dietary exposure assessment was not conducted. The chronic dietary risk assessment was conducted, and the assessment is partially refined, yet conservative. The overall chronic dietary risks from residues in foods are less than 1% of the cPAD for the general U.S. population. The most highly exposed population subgroup is all infants < 1 year, which occupies 1.4% of the cPAD. These values do not exceed HED's level of concern.

The HIARC classified fluthiacet-methyl as likely to be a human carcinogen, and therefore, quantification of human cancer risk is required. The overall cancer dietary risk for the U.S. population is 7.51×10^{-7}, which does not exceed HED's level of concern.

Table 5.1.2. Summary of Dietary Exposure and Risk for Fluthiacet-methyl

Population Subgroup	Chronic Dietary		Cancer	
	Dietary Exposure (mg/kg/day)	% cPAD[1]	Dietary Exposure (mg/kg/day)	Risk[2]
General U.S. Population	0.0000050	< 1%	0.000004	7.51×10^{-7}
All Infants (< 1 year old)	**0.000014**	**1.4 %**	N/A	N/A
Children 1-2 years old	0.0000070	< 1%		
Children 3-5 years old	0.0000070	< 1%		
Children 6-12 years old	0.0000050	< 1%		
Youth 13-19 years old	0.0000040	< 1%		
Adults 20-49 years old	0.0000040	< 1%		
Adults 50+ years old	0.0000040	< 1%		
Females 13-49 years old	0.0000040	< 1%		

[1] cPAD = 0.001 mg/kg/day
[2] $Q_1^* = 0.207$ (mg/kg/day)$^{-1}$

Although dietary risks are minimal, it is important to note that 1.) drinking water (EDWCs) drives

the dietary exposure estimates, accounting for the majority of each exposure estimate; and 2.) the EDWCs are highly conservative.

5.2 Residential (Non-Occupational) Exposure/Risk Pathway

There are no existing or proposed residential uses for this product. However, 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 groundboom application. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new database submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

6.0 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. 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.

For fluthiacet-methyl there are no residential uses, and therefore, the aggregate assessment includes only food and drinking water exposures. Furthermore, since the chronic and cancer dietary assessment incorporated drinking water, the dietary exposure and risk estimates are equivalent to the aggregate exposure and risk estimates. Drinking water was included in the dietary assessment by using the relevant PRZM-EXAMS value as a residue for water (all sources) in the dietary exposure assessment. The principal advantage of this approach 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. **The overall chronic and cancer aggregate risks do not exceed HED's level of concern. For details, refer to Section 5.0.**

7.0 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 fluthiacet-methyl and any other substances and fluthiacet-methyl 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 fluthiacet-methyl 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/.

8.0 Occupational Exposure/Risk Pathway

Reference:
Occupational Risk Assessment to Support Request for a Section 3 Registration of Fluthiacet-methyl on Cotton, Barry O'Keefe, 10/11/05, D321648.

8.1 Short/Intermediate-Term and Cancer Handler Risk

There is a potential for exposure to fluthiacet-methyl during handling (*i.e.*, mixing, loading, and application) and postapplication activities. An exposure/risk assessment using applicable endpoints selected by the RAB3 Toxicology Team, HIARC, and CARC was performed. Handler's inhalation exposure and risk were estimated for the following scenarios: 1) open mixing/loading liquid to support groundboom application; 2) open mixing/loading liquid to support aerial application; 3) groundboom application with an open cab; 4) aerial application with enclosed cockpit; and 5) flagger for aerial applications. The proposed label prohibits application by irrigation methods.

No chemical-specific handler exposure data were submitted in support of this proposed Section 3 registration. It is the policy of the HED to use data from the PHED Version 1.1, as presented in PHED Surrogate Exposure Guide (8/98) to assess handler exposures for regulatory actions when chemical-specific monitoring data are not available (HED Science Advisory Council for Exposure Draft Policy # 7, dated 1/28/99). HED believes the use of the Surrogate Exposure Guide provides a more reliable exposure estimate than individual subsets because of the larger number of replicates in the pooled data. Therefore, HED performed its analysis of occupational handlers using the PHED surrogate table for unit exposure values. Also used were HED standard values for acres treated per day, body weight, and the level of personal protective equipment to assess handler exposures. The unit exposure values from PHED are considered to be central tendency. The application rates, treatment variables, *etc.* used in this assessment are upper percentile values. Therefore, the potential dose is characterized as central to high-end.

The minimum level of PPE for handlers under the Worker Protection Standard (WPS) is based on acute toxicity for the end-use product. The Registration Division (RD) is responsible for ensuring that PPE listed on the label is in compliance with the WPS. The proposed label lists PPE for handlers as follows: long-sleeved shirt and long pants; chemical-resistant gloves such as barrier laminate, butyl rubber ≥ 14 mils, or Viton ≥ 14 mils; shoes plus socks; and protective eyewear (goggles or face shield).

Table 8.1a summarizes exposure assumptions and non-cancer risk estimates for occupational handlers. With only baseline PPE (no respirator), the non-cancer inhalation risk estimates for all handler scenarios resulted in margins of exposure (MOEs) ≥100, and therefore do not exceed

HED's level of concern.

Table 8.1a Occupational Handler Non-Cancer Baseline Exposure and Risk Estimates for Fluthiacet-methyl.

Exposure Scenario (Unit exposure from PHED unless otherwise indicated)	Crop	Application Rate (lb ai/A)	Amount Treated per day (acres)	Exposure Route	Unit Exposure (mg/lb ai)	Data Confidence	Daily Dose[1] (mg/kg/day)	MOE[2]
(1) M/L Liquids: Open mixing (groundboom)	Cotton	0.0064	200	Inhalation	0.0012	High	2.19E-5	59,000
(2) M/L Liquids: Open mixing (aerial)	Cotton	0.0064	1200	Inhalation	0.0012	High	1.32E-4	9,900
(3) Apply Liquids: groundboom (open cab)	Cotton	0.0064	200	Inhalation	0.00074	High	1.35E-5	96,000
(4) Apply Liquids: aerial (enclosed cockpit)	Cotton	0.0064	1200	Inhalation	0.000068	Medium	7.46E-6	170,000
(5) Flagging Liquids: aerially applied	Cotton	0.0064	350	Inhalation	0.00035	High	1.12E-5	120,000

[1] Daily Dose = [Application Rate * Amount Treated * Unit Exposure (mg/lb ai handled) * Absorption Factor (100%)]/Body Weight (70 kg)
[2] MOE = NOAEL/Daily Dose. The oral NOAEL of 1.3 mg/kg/day was used for all calculations.

To quantify cancer risk, the Q_1* is multiplied by the estimated Lifetime Average Daily Doses (LADDs) from occupational exposure. Dermal doses are first adjusted for dermal absorption (*i.e.*, 31%), because the Q_1* is based on an oral study. Inhalation doses are assumed to be 100% absorbed. Cancer risks for handlers and postapplication workers that exceed 10^{-4} are of concern, and require measures such as additional PPE or engineering controls to mitigate exposure, with the goal of achieving a risk level of 10^{-6} or less.

Exposure assumptions and cancer risk estimates for occupational handlers are summarized in Tables 8.1b and 8.1c. The proposed label stipulates baseline clothing plus gloves and application rates from 0.00427 to 0.00640 lb ai/A. The standard practice of HED is to use typical application rates for assessing cancer risks. However, a typical application rate was not provided, nor can one be determined by available information; therefore, cancer handler risk estimates were first calculated using the maximum application rate of 0.0064 lb ai/A (see Table 8.1b). For the scenario of groundboom applications, cancer risk levels of 10^{-6} or less were achieved for mixers/loaders and applicators with baseline clothing plus gloves. For flaggers of aerial applications, cancer risk levels of 10^{-6} or less were also achieved. However, for the scenario of aerial applications, cancer risk levels of 10^{-6} or less were not achieved for mixers/loaders or applicators, even with the addition of full personal protective equipment (PPE) and/or engineering controls. Since aerial application scenarios failed to achieve cancer risk levels of 10^{-6} or less at the maximum application rate, the lower application rate of 0.00427 lb ai/A was also used to calculate cancer handler risk estimates (see Table 8.1c), *i.e.*, for risk management purposes. However, cancer risk levels of 10^{-6} or less were still not achieved for mixers/loaders, even with

the addition of full PPE, but were achieved for applicators using engineering controls. For those scenarios where the estimated handler cancer risks are in the 10^{-6} to 10^{-4} range it would be warranted to seek ways of cost-effectively reducing risks, such as increased levels of personal protection, as is commonly applied with non-cancer risk estimates (*i.e.*, additional PPE or engineering controls). Adding gloves for mixer/loader exposure scenarios gives the most significant reduction in exposure.

Table 8.1b Occupational Handler Cancer Exposure and Risk Estimates for Fluthiacet-Methyl Using Maximum Application Rate.

PHED Scenarios	Application Rate[1] (lb ai/A)	Area Treated (Acres)	PHED Unit Exposure[2] (mg/lb ai)	Daily Dose[3] (mg/kg/day)	LADD[4] (mg/kg/day)	Cancer Risk[5]
(1) Mix/Load Liquids: Open mixing (groundboom)	0.0064	200	Dermal: 2.9	1.65E-2	6.79E-4	**1.4E-4**
			Dermal: 0.023 (w/ gloves)	1.30E-4	6.24E-6 (w/ gloves)	**1.3E-6 (w/ gloves)**
			Dermal: 0.017 (w/ gloves & DL)	9.64E-5		
			Inhalation: 0.0012	2.19E-5	4.86E-6 (gloves & DL)	1.0E-6 (gloves & DL)
(2) Mix/Load Liquids: Open mixing (aerial)	0.0064	1200	Dermal: 2.9	9.87E-2	4.06E-3	**8.4E-4**
			Dermal: 0.023 (w/ gloves)	7.82E-4	3.76E-5 (w/ gloves)	**7.8E-6 (w/ gloves)**
			Dermal: 0.017 (w/ gloves & DL)	5.79E-4	2.92E-5 (gloves & DL)	**6.0E-6 (gloves & DL)**
			Inhalation: 0.0012	1.32E-4	2.41E-5 (gloves, DL & respirator)	**5.0E-6 (gloves, DL & respirator)**
			Inhalation: 0.00024 (w/ respirator)	2.63E-5		
(3) Apply Liquids: groundboom (open cab)	0.0064	200	Dermal: 0.014	7.93E-5	3.82E-6	7.9E-7
			Inhalation: 0.00074	1.35E-5		
(4) Apply Liquids: aerial (closed cab)	0.0064	1200	Dermal: 0.005	1.71E-4	7.32E-6	**1.5E-6**
			Inhalation: 0.000068	7.46E-6		
(5) Flagging Liquids: aerially applied	0.0064	350	Dermal: 0.011	1.09E-4	4.94E-6	1.0E-6
			Inhalation: 0.00035	1.12E-5		

[1] Maximum proposed application rate for cancer assessment.
[2] PHED Unit Exposure values are for baseline protection (long-sleeved shirt, long pants, shoes plus socks) unless otherwise indicted; DL = double layer or coveralls.
[3] Daily Dose =(Unit Exposure x Application Rate x Area Treated x Absorption Rate (31% for dermal & 100% for inhalation))/Body Weight.
[4] LADD = [Dermal Daily Dose + Inhalation Daily Dose] * (30 days worked per year / 365 days) * (35 years worked / 70-yr lifetime).
[5] Cancer Risk = LADD (mg/kg/day) * (Q_1*), where Q_1* = 0.207 (mg/kg/day)$^{-1}$.

Table 8.1c. Occupational Handler Cancer Exposure and Risk Estimates for Fluthiacet-Methyl Using Minimum Application Rate.

PHED Scenarios	Application Rate[1] (lb ai/A)	Area Treated (Acres)	PHED Unit Exposure[2] (mg/lb ai)	Daily Dose[3] (mg/kg/day)	LADD[4] (mg/kg/day)	Cancer Risk[5]
(1) Mix/Load Liquids: Open mixing (groundboom)	0.00427	200	Dermal: 2.9	1.10E-2	4.53E-4	**9.4E-5**
			Dermal: 0.023 (w/ gloves)	8.69E-5	4.17E-6 (w/ gloves)	8.6E-7 (w/ gloves)
			Inhalation: 0.0012	1.46E-5		
(2) Mix/Load Liquids: Open mixing (aerial)	0.00427	1200	Dermal: 2.9	6.58E-2	2.70E-3	**5.6E-4**
			Dermal: 0.023 (w/ gloves)	5.21E-4	2.50E-5 (w/ gloves)	**5.2E-6 (w/ gloves)**
			Dermal: 0.017 (w/ gloves & DL)	3.83E-4	1.93E-5 (gloves & DL)	**4.0E-6 (gloves & DL)**
			Inhalation: 0.0012	8.78E-5		
			Inhalation: 0.00024 (w/ respirator)	1.76E-5	1.65E-5 (gloves, DL & respirator)	**3.4E-6 (gloves, DL & respirator)**
(3) Apply Liquids: groundboom (open cab)	0.00427	200	Dermal: 0.014	5.29E-5	2.54E-6	5.3E-7
			Inhalation: 0.00074	9.01E-6		
(4) Apply Liquids: aerial (closed cab)	0.00427	1200	Dermal: 0.005	1.13E-4	4.85E-6	1.0E-6
			Inhalation: 0.000068	4.98E-6		
(5) Flagging Liquids: aerially applied	0.00427	350	Dermal: 0.011	7.27E-5	3.29E-6	6.8E-7
			Inhalation: 0.00035	7.47E-6		

[1] Minimum application rate for cancer assessment.
[2] PHED Unit Exposure values are for baseline protection (long-sleeved shirt, long pants, shoes plus socks) unless otherwise indicted; DL = double layer or coveralls.
[3] Daily Dose =(Unit Exposure x Application Rate x Area Treated x Absorption Rate (31% for dermal & 100% for inhalation))/Body Weight.
[4] LADD = [Dermal Daily Dose + Inhalation Daily Dose] * (30 days worked per year / 365 days) * (35 years worked / 70-yr lifetime).
[5] Cancer Risk = LADD (mg/kg/day) * (Q_1*), where Q_1* = 0.207 (mg/kg/day)$^{-1}$.

8.2 Short/Intermediate/Long-Term Postapplication Risk

This proposed Section 3 action on fluthiacet-methyl involves foliar applications to cotton. Therefore, there is a potential for short- and intermediate-term dermal exposure to workers entering fluthiacet-methyl treated areas to perform a variety of agricultural/occupational tasks, and a risk assessment is required. However, no non-cancer short- or intermediate-term dermal endpoints were established for fluthiacet-methyl; and therefore, no non-cancer short- or intermediate-term dermal postapplication risk was assessed. Inhalation exposure is expected to be negligible for postapplication scenarios.

Since a Q^* has been established for fluthiacet-methyl, postapplication cancer occupational risks from working in cotton fields treated with fluthiacet-methyl were assessed. However, since the proposed use pattern is as a defoliant, only minimal exposure to postapplication workers is expected. The postapplication worker activities of irrigating or weeding are not expected to occur after applications of fluthiacet-methyl, since harvesting should occur very soon after application. Cotton is assumed to be mechanically harvested. The Agency acknowledges that there is some

potential for exposure even during mechanical harvesting because individuals engaged in fully mechanized activities have short-term excursions from the protected area for various reasons (*e.g.*, unclogging machinery or equipment inspection for breakage). In these cases, the WPS § 170.112(c) exception for short-term activities applies. The postapplication activity of scouting was assessed, since two applications of fluthiacet-methyl are allowed by the proposed label, and scouters may enter treated fields to assess how efficacious the pesticide application has been. However, the exposure potential should be minimal, since the foliage should be desiccated or removed (*i.e.*, defoliated). Therefore, the transfer coefficient used for scouting plants with minimum foliage was 100 cm^2/hr, rather than 1500 cm^2/hr.

Chemical-specific postapplication exposure data were not provided. The transfer coefficient used in this assessment is from an interim transfer coefficient policy developed by HED's Science Advisory Council for Exposure using proprietary data from the Agricultural Re-entry Task Force (ARTF) database (policy # 3.1). It is the intention of the HED Exposure SAC that this policy be periodically updated to incorporate additional information about agricultural practices in crops and new data on transfer coefficients. Much of this information will originate from exposure studies currently being conducted by the ARTF, from further analysis of studies already submitted to the Agency, and from the studies in the published scientific literature. Likewise, because chemical-specific dissipation data were not submitted, it is the HED policy, for calculating postapplication exposure and risk, to assume that 20% of the application rate is available to dislodge on the day of treatment, and that this residue dissipates at a rate of 10% per day, thereafter. While the transfer coefficients and dislodgeable residue dissipation variables are considered to be average values, the high-end application rate results in a daily postapplication dose that is characterized as high-end.

Inputs and calculated postapplication risk estimates in cotton fields treated with fluthiacet-methyl can be seen in Table 8.2. Risk calculations for postapplication workers scouting in cotton fields on the day of application result in a **cancer risk of 4.3 x 10^{-7} using the maximum application rate. Therefore, the cancer risk does not exceed HED's level of concern.**

The restricted entry interval (REI) under the Worker Protection Standard (WPS) is based on the acute toxicity of technical grade fluthiacet-methyl, which is classified in acute toxicity category III/IV. Acute toxicity category III chemicals require a 12-hour REI. Thus, the 12-hour REI that appears on the Appeal™ label is appropriate under the WPS.

Table 8.2. Cancer Exposure and Risk for Occupational Postapplication Activities

Activity	Application Rate[1] (lb ai/A)	Dislodgeable Foliar Residue[2] (ug/cm^2)	Dermal Transfer Coefficient (cm^2/hr)	Post-application Day (t)	Daily Dose[3] (mg/kg/day)	Days Worked per Year	LADD[4] (mg/kg/day)	Cancer Risk[5]
Scouting	0.00540	0.01	100	0	5.09E-5	30	2.09E-6	4.3E-7
Scouting	0.00427	0.01	100	0	3.39E-5	30	1.39E-6	2.9E-7

[1] Minimum and maximum application rate for cancer assessment.
[2] Dislodgeable Foliar Residue = Application rate (lb ai/A) x CF (4.54E+8 ug/lb) x CF (2.47E-8 A/cm^2) x 0.2
[3] Daily Dose = (Dislodgeable Foliar Residue x Dermal Transfer Coefficient x Exposure Time (8 hr) x Dermal Absorption Factor (0.31)) / (CF: 1000 ug/mg) x Body weight.
[4] LADD = (Daily Dose) * (No. days worked per year (30) / 365 days) * (35 years worked / 70-yr lifetime).
[5] Cancer Risk = LADD (mg/kg/day) * (Q_1*), where Q_1* = 0.207 (mg/kg/day)$^{-1}$.

9.0 Data Needs and Label Recommendations

9.1 Toxicology

Although the inhalation risk assessments in this document rely on oral studies, and by default require an inhalation toxicity study, the requirement for an inhalation toxicity study is waived based on Criterion 4 of the August 15, 2002 *HED Guidance: Waiver Criteria for Multiple-Exposure Inhalation Toxicity Studies*. Fluthiacet-methyl is classified as Toxicity Category IV for acute inhalation toxicity, and the occupational inhalation MOEs are greater than 1000 (Criterion 4).

9.2 Residue Chemistry

860.1200 Directions for Use

- Because the petitioner has not submitted crop field trial data from Region 10, the product label must be amended to state that application may not be made to cotton grown in Arizona or California. Accordingly, a revised Section B (labels) is required.

860.1650 Submittal of Analytical Reference Standards

- Analytical reference standards of fluthiacet-methyl and CGA-300402 must be supplied and supplies replenished as requested by the Repository. The reference standards should be sent to the Analytical Chemistry Lab, to the attention of either Theresa Cole or Frederic Siegelman [USEPA, National Pesticide Standards Repository/Analytical Chemistry Branch/OPP, 701 Mapes Road, Fort George G. Meade, MD 20755-5350].

860.1550 Proposed Tolerances

- A tolerance must be proposed for residues in/on undelinted cotton seed; the available data indicate that a tolerance of 0.02 ppm (combined LOQs) is appropriate.

- The available data indicate that the proposed tolerance for residues in/on gin byproducts is too high; a revised tolerance of 0.20 ppm should be proposed.

Accordingly, a revised Section F is required. All outstanding data requirements specified in conclusions 2, 8c, 10b, 11b, 13b, 13c, 13d, 14b. 14c, 14d, 15, 16c, 16d, and 19 of the previous PP#7F4821 review have been addressed or fulfilled. The requirement to submit the final report of the livestock commodity storage stability study, conclusion 12a of the previous review, has not been fulfilled and remains outstanding.

9.3 Occupational and Residential Exposure

As outlined in Section 8.1, certain occupational exposure scenarios result in estimated handler cancer risks in the 10^{-6} to 10^{-4} range. In these cases, it would be warranted to seek ways of cost-effectively reducing risks, such as increased levels of personal protection, as is commonly applied

with non-cancer risk estimates (*i.e.*, additional PPE [gloves are recommended because they give the most significant reduction in exposure] or engineering controls).

References:

CGA-248757: Review of a Guideline Metabolism Study, MRID 438300-18, -19 and -20, Timothy McMahon, 10/18/96, D224320.

PP#7F4821; Fluthiacet-methyl (Action Herbicide, EPA Reg. No. 100-805) in/on Field Corn, Pop Corn, Sweet Corn, and Cotton. Briefing Memorandum for Metabolism Assessment Review Committee, William Wassell, 10/25/2000, D268759.

PP#7F4821; Fluthiacet-methyl in/on Field Corn, Sweet Corn, Pop Corn and Cotton. Conclusions of the 10/31/2000 Meeting of the Metabolism Assessment Review Committee, William Wassell, 2/6/01, D272221

PP#7F4821; Fluthiacet-methyl in/on Field Corn, Sweet Corn, Pop Corn and Cotton. Evaluation of Metabolism Data, Magnitude of Residue Data, and Analytical Methodology, William Wassell, 2/20/01, D234717, D234495, D238930, D239384, D249645, D257126.

Fluthiacet-methyl. Petition for the Establishment of Tolerances for Use on Field Corn, Sweet Corn, Pop Corn, and Cotton. Submission of Residue Analytical Method, Multiresidue Method, and Crop Field Trial Data for Cotton. PP#7F4821, Michael Doherty, 11/22/05, D304795

Review of New Use for Fluthiacet-methyl (Appeal EC; previously identified as CGA248757) as a defoliant in cotton, Keara Moore, 11/1/05, D304797.

PP#7F821 Fluthiacet-methyl (CGA-248757; Action™) on Sweet Corn, Field Corn and Pop Corn Human Health Risk Assessment, 9/4/2001, W. Wassell, D277296

Fluthiacet-methyl: Chronic and Cancer Dietary Exposure Assessment for the Section 3 Registration Action of Fluthiacet-methyl on Cotton, Sarah Winfield, 12/5/05, D323703.

Usage Report in Support of Registration for the Defoliant Fluthiacet-Methyl (PC 108803) on Cotton, Alan Halvorson, 11/4/05, D323281.

Pesticide Fact Sheet: Fluthiacet-methyl, USEPA, April 1999, http://www.epa.gov/opprd001/factsheets/fluthiacet.pdf

Fluthiacet-methyl (CGA-248-757; ActionTM) - Report of the Hazard Identification Assessment Review Committee, Alan C. Levy, 6/16/98, HED Doc. No. 012644

Evaluation of the Carcinogenic Potential of Fluthiacet-methyl, CARC Final Report, A. Levy and J. Rowland, 11/20/98, HED Doc. No. 012784.

Fluthiacet-methyl (CGA-248757; ActionTM) - REVISED Report of the FQPA Safety Factor

Committee, 6/11/98, TXR No.012643.

Occupational Risk Assessment to Support Request for a Section 3 Registration of Fluthiacet-methyl on Cotton, Barry O'Keefe, 10/11/05, D321648.

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