



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

OFFICE OF PREVENTION, PESTICIDES  
AND TOXIC SUBSTANCES

February 28, 2007

**MEMORANDUM**

**SUBJECT:** **Fomesafen Sodium:** HED Registration Review Problem Formulation Document.  
PC Code:123802, DP Barcode: D306022.

**FROM:** Whang Phang, Toxicologist  
Reregistration Branch 1  
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**THROUGH:** Michael S. Metzger, Branch Chief  
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**TO:** Wilhelmena Livingston, Chemical Review Manager  
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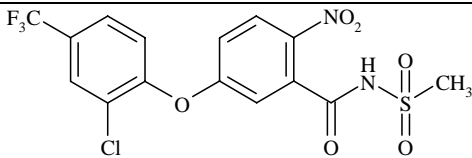
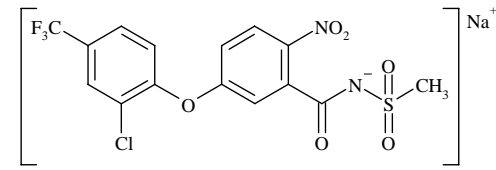
Attached is the Health Effects Division chapter of the fomesafen sodium problem formulation document in supporting the registration review of this chemical.

## Section 1. Introduction

The HED Fomesafen Registration Review Team has evaluated the human health assessments for the herbicide fomesafen to determine the scope of work necessary to support the registration review. The team considered the current use profile, the toxicity, and exposure databases for this chemical. The primary source for the status update was the most recent HED human health risk assessment (Donna Davis, D325797, 2/28/06). The purpose of this screen is to determine whether sufficient data are available to assess the safety of this pesticide and whether any new data have been submitted since the last assessment which would necessitate conducting a new human health risk assessment to support registration review. A comprehensive listing of the documents considered is presented in Section 12 of this document. The HED Registration Review team includes Donna Davis, Toiya Goodlow, Matt Lloyd, and Whang Phang.

Fomesafen is currently registered for use on several crops including cotton, dry beans, snap beans, and soybeans. Tolerances are established in 40 CFR 180.433 for these commodities. Fomesafen is not registered for use on any sites that would result in residential exposure.

## Section 2. Chemical Identity

<b>Table 1. Fomesafen and its Sodium Salt Nomenclature</b>	
Chemical structure	
Common name	Fomesafen
Molecular formula	C <sub>15</sub> H <sub>10</sub> ClF <sub>3</sub> N <sub>2</sub> O <sub>6</sub> S
Molecular weight	438.77
PC Code	N/A
IUPAC name	5-(2-chloro- $\alpha,\alpha,\alpha$ -trifluoro-p-tolyloxy)-N-methylsulfonyl-2-nitrobenzamide
CAS name	5-[2-chloro-4-(trifluoromethyl)phenoxy]-N-(methylsulfonyl)-2-nitrobenzamide
CAS registry number	72178-02-0
Chemical structure	
Common name	Sodium salt of fomesafen
Molecular formula	C <sub>15</sub> H <sub>9</sub> ClF <sub>3</sub> NaN <sub>2</sub> O <sub>6</sub> S
Molecular weight	460.75
PC Code	123802
IUPAC name	5-(2-chloro- $\alpha,\alpha,\alpha$ -trifluoro-p-tolyloxy)-N-methylsulfonyl-2-nitrobenzamide, sodium salt
CAS name	5-[2-chloro-4-(trifluoromethyl)phenoxy]-N-(methylsulfonyl)-2-nitro-benzamide, sodium salt
CAS registry number	108731-70-0

### Section 3. Toxicology

Fomesafen has low acute toxicity by oral route of exposure. It is severely irritating to the eye and is a moderate skin irritant. In the subchronic and chronic feeding studies, the consistent finding is the effect in the liver characterized by increases in liver weight and in associated enzymes including alkaline phosphatase, alanine transaminase, and aspartate transaminase. Hyalinization of the liver is also observed.

Currently, the toxicity database is adequate in establishing the toxicity endpoints for risk assessment. No toxicity studies have been received since the last human health risk assessment (D. Davis, D325797, 2/28/06). Acute inhalation and dermal toxicity studies and a skin sensitization study were identified as data gaps.

The risk assessment team has reevaluated the toxicity endpoints and doses according to the current policies on selecting toxicity endpoints and uncertainty factors. These conclusions are summarized below.

**Cancer classification:** The Cancer Assessment Review Committee (CARC) has classified fomesafen as “Not Likely to be Carcinogenic to Humans”. A quantitative cancer risk assessment is not needed.

**FQPA safety factor:** Based on the available toxicology data, the fomesafen risk assessment team recommended the FQPA SF be reduced to 1x because there was no concern and/or residual uncertainty with regard to pre- and/or postnatal toxicity. Since no new data are available to necessitate any changes to this conclusion and it concurs with the current FQPA policy, the conclusion remains unchanged.

<b>Table 2. Summary of Toxicological Doses and Endpoints for Fomesafen for Use in Human Risk Assessments</b>				
<b>Exposure Scenario</b>	<b>Point of Departure</b>	<b>Uncertainty/ FQPA Safety Factor</b>	<b>RfD, PAD, Level of Concern for RA</b>	<b>Study and Toxicological Effects</b>
Acute Dietary (females 13-49) and General population	No toxic effects attributable to a single dose of fomesafen were found in the database.			
Chronic Dietary (all populations)	NOAEL = 0.25 mg/kg/day	UF <sub>A</sub> = 10x UH <sub>H</sub> = 10x FQPA SF = 1x	RfD = 0.0025 mg/kg/day  cPAD = 0.0025 mg/kg/day	Chronic toxicity - rat LOAEL = 5 mg/kg/day based on hyalinization of the liver in males
Dermal Short-Term (1-30 days) and Intermediate-Term (1-6 months)	NOAEL = 100 mg/kg/day  (Dermal absorption rate = 20%)*	UF <sub>A</sub> = 10x UH <sub>H</sub> = 10x FQPA SF = 1x	LOC for MOE = 100 (Occupational)	Prenatal developmental – rat LOAEL = 200 mg/kg/day based on postimplantation loss

<b>Exposure Scenario</b>	<b>Point of Departure</b>	<b>Uncertainty/ FQPA Safety Factor</b>	<b>RfD, PAD, Level of Concern for RA</b>	<b>Study and Toxicological Effects</b>
Inhalation Short-Term (1 - 30 days) and Intermediate-Term (1-6 months)	NOAEL = 0.5 mg/kg/day  (Inhalation adsorption rate = 100% oral equivalent)	UF <sub>A</sub> = 10x UH <sub>H</sub> = 10x FQPA SF = 1x	LOC for MOE = 100 (Occupational)	90-Day - rat LOAEL = 10 mg/kg/day based on hyalinization of hepatocytes, increased eosinophilia, reduced granulation, increased liver weights in males and females, and increases in plasma alkaline phosphatase, alanine transaminase and aspartate transaminase in males.
Cancer Classification	"Not Likely to be Carcinogenic to Humans."			

NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF<sub>A</sub> = extrapolation from animal to human (interspecies). UH<sub>H</sub> = potential variation in sensitivity among members of human population (intraspecies). FQPA SF= FQPA safety factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. RA = risk assessment

\* = The dermal absorption factor was estimated to be 20% based on the results of structurally related chemicals: acifluorfen (20% absorption rate) and oxifluorfen (18% absorption rate).

### Section 3. Residue Chemistry

The residue chemistry database is essentially complete except for supporting data required as a condition of registration for certain new uses (D. Davis, D325797, 2/28/2006). The supporting data are listed in the Attachment.

### Section 4. Dietary Exposure

Acute dietary risk assessments were not required as there were no endpoints identified attributable to a single exposure of fomesafen. Chronic dietary risk assessments were conducted for fomesafen sodium using the Dietary Exposure Evaluation Model (DEEM-FCID™), Version 2.03, which used food consumption data from the United States Department of Agriculture's (USDA's) Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. The assumptions of these assessments were tolerance level residues and 100% crop treated. The highest exposure and risk estimates based on exposure from food only were for the "children 1 - 2 years" population subgroup. The exposure for food was 0.000041 mg/kg/day, which utilized 1.6% of the cPAD (chronic population adjusted dose).

### Section 5. Aggregate and Cumulative Exposure

There are no residential uses formulated with fomesafen. Therefore, the aggregate assessment considers only chronic exposure for food and drinking water.

An aggregate dietary assessment using DEEM-FCID™ was conducted in which the estimated drinking water concentrations (EDWCs) for ground and surface water from the Environmental

Fate and Effects Division were included directly in the assessment (Table 3). The dietary exposure analyses in this assessment resulted in chronic dietary risk estimates for food and water that were below the Agency’s level of concern. The highest exposure and risk estimates were for the “all infants” population subgroup. The exposure for food plus surface water was 0.000766 mg/kg/day, which utilized 31% of the cPAD; and the exposure for food plus ground water was 0.000107 mg/kg/day, which utilized 4.3% of the cPAD.

Population Subgroup <sup>1</sup>	Surface Water			Ground Water		
	EDWC (ppb)	Exposure (mg/kg/day)	% cPAD	EDWC (ppb)	Exposure (mg/kg/day)	% cPAD
General U.S. Population	10.535	0.000239	9.5	1.0	0.000038	1.5
<b>All Infants (&lt; 1 year old)</b>	10.535	<b>0.000766</b>	<b>31</b>	1.0	<b>0.000107</b>	<b>4.3</b>
Children 1-2 years old	10.535	0.000371	15	1.0	0.000072	2.9
Children 3-5 years old	10.535	0.000344	14	1.0	0.000064	2.6
Children 6-12 years old	10.535	0.000236	9.4	1.0	0.000044	1.7
Youth 13-19 years old	10.535	0.000175	7.0	1.0	0.000030	1.2
Adults 20-49 years old	10.535	0.000221	8.8	1.0	0.000033	1.3
Adults 50+ years old	10.535	0.000231	9.2	1.0	0.000033	1.3
Females 13-49 years old	10.535	0.000219	8.8	1.0	0.000032	1.3

<sup>1</sup> The values for the population with the highest dietary exposure and risk estimates are bolded.

## Section 6. Occupational Exposure

There is potential for occupational exposure to fomesafen during mixing, loading, application, and postapplication activities. The occupational database is adequate, and all relevant occupational scenarios are assessed for all existing uses. The latest risk assessment (M. Lloyd, D294458, 215/2006) indicated most of the occupational scenarios did not result in risks of concern, with the exception of inhalation risks to mixer/loader scenario for aerial application. Inhalation MOEs for the mixer/loader scenarios for aerial application were of concern with baseline PPE (includes long-sleeve shirt, long pants, and gloves). PF5 respirators are required to achieve acceptable MOEs (i.e., greater than the target MOE of 100). All of the dermal MOEs are greater than the target MOE of 100 with single layer PPE for handlers and baseline PPE for applicators and flaggers. Single layer PPE is mandated on the proposed fomesafen label under consideration. All of the post-application MOEs are greater than 100 on Day 0, and the risks are not of concern.

## Section 7. Incident Report of human Health Effects Caused by Fomesafen.

The available incident report data bases (1982 to the present) indicate skin irritation in four cases and no reports of other ill effects (M. S. Hawkins, D331945, 7/25/2006).

## Section 8. Anticipated Data Needs

HED anticipates that a revised risk assessment for fomesafen will not be needed for registration review. Additional data have been previously required as conditions of registration for certain new uses. These are listed in the Attachment to this document for informational purposes.

## Section 10. Tolerances

Tolerances are established under 40 CFR §180.433 for the residues of fomesafen 5-[2-chloro-4-(trifluoromethyl) phenoxy]-N-(methylsulfonyl)-2-nitrobenzamide from the application of its sodium salt as shown in the table below.

No Codex maximum residue limits (MRLs) have been established for residues of fomesafen. Canadian MRLs have been established for residues of fomesafen in/on dry beans, lima beans, snap beans, and soybeans at 0.05 ppm.

Commodity	U.S. (ppm)	Codex (mg/kg)	Canada (ppm)
Soybean	0.050		0.05
Cotton, undelineated seed	0.025		
Cotton, gin byproducts	0.025		
Bean dry	0.025		0.05
Bean, snap, succulent	0.025		0.05
Lima beans			0.05

## Section 11. Overall Conclusions

HED anticipates no additional human health risk assessments will be needed for the existing uses of fomesafen.

## Section 12. Reference Memoranda

The memoranda listed in the following table were considered in the development of this document.

HED Memoranda Relevant to Registration Review			
Author	Barcode	Date	
D. Davis	D325797	2/28/06	Fomesafen Sodium. Human Health Risk Assessment for a Proposal to Amend Use on Soybeans, and Proposal to Add uses on Cotton, Dry Bean, and Snap Bean.
D. Davis		4/25/06	Fomesafen Sodium. Addendum to the 2/28/02 Human Health Risk Assessment for a Proposal to Amend Use on Soybeans, and Proposal to Add uses on Cotton, Dry Bean, and Snap Bean.
J. Kidwell	TXR # 0053835	11/3/05	Second report of the Cancer Assessment Review Committee
M. Lloyd	D294458	2/15/06	Fomesafen: Occupational and Residential Exposure and Risk assessment for the Registration for New Uses on Dry Beans, Snap Beans, and Cotton.
T. Goodlow	D325798	2/15/06	Chronic Dietary Exposure Assessment for the HED Human Health Risk Assessment.

<b>HED Memoranda Relevant to Registration Review</b>			
<b>Author</b>	<b>Barcode</b>	<b>Date</b>	
W. Greear	TXR # 0052977	1/20/06	Fomesafen: Toxicological Assessment for Incorporation into Risk Assessment Document.
D. Davis	D325801	4/25/06	Fomesafen Sodium: Residue Chemistry Summary for Human Health Risk Assessment, a Proposal to Amend use on Soybeans, and Proposals to Add uses on Cotton, Dry Bean, and Snap Bean.
J. Hetrick	D314014	9/27/05	Tier II Drinking water Assessment for Fomesafen use on cotton, soybeans, dry beans, and snap beans.

## Attachment

This list represents data previously required as a condition of registration for certain new uses. This is provided for information purposes only.

1. Upgrade the cotton metabolism study with additional information (actual application rate for higher treatment rate, date of sample analysis).
2. Submit raw data to support the submitted method validation data.
3. Modifications for enforcement method to incorporate specific information on dry bean, snap bean, and soybean aspirated fraction.
4. Submit multiresidue method testing data for fomesafen.
5. Data on the stability of residues of fomesafen in/on cotton gin byproducts, soybean hulls and oil, and field corn or sorghum forage & stover.
6. Additional data to upgrade the available cotton crop field trial data including soil characteristic data, summary of weather conditions at individual sites, indications as to whether irrigation was used, & average historical data for temperature & rainfall for the duration of the field trial intervals.

Guideline 869.1200	Acute dermal toxicity study
Guideline 870.1300	Acute inhalation toxicity study
Guideline 869.2600	Skin sensitization study