UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: **2/28/06**

MEMORANDUM:

SUBJECT: Fomesafen Sodium. Human Health Risk Assessment for a Proposal To Amend Use on Soybeans, and Proposals to Add Uses on Cotton, Dry Bean, and Snap Bean. PC Code: 123802, Petition Nos: 1E6228, 9F5068, 6E4653, DP Barcode: D325797.

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

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Attached is the Human Health Risk Assessment for Fomesafen Sodium to support a proposal to amend the use on soybeans and to support PP# 1E6228, 9F5068 and 6E4653.

cc: D. Davis/HED/RRB1.

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1.0 Executive Summary

Fomesafen sodium is a contact herbicide for postemergent control of broadleaf weeds. Fomesafen products are formulated as the sodium salt and the concentration of the active ingredient in the formulation is expressed in terms of the acid equivalent (ae). Fomesafen sodium is in the diphenylether chemical class and it mode of action is via inhibition of protoporphyrinogen oxidase (PPO) in the plant.

Fomesafen sodium is currently registered for use on soybeans and the registrant, Syngenta, is proposing the addition of a later season application to soybeans, revisions to the soybean tolerances based on new methodology with lower detection limits, revision of rotational crop restrictions and a new use on cotton. Additionally, the Interregional Research Project No. 4 (IR-4) has petitioned for new uses on dry beans and snap beans. For soybeans, the amended action would permit application at a maximum seasonal rate of 0.375 lbs ae/A up to 45 days prior to harvest. The cotton proposed use would allow application of fomesafen at a rate of 0.5 lbs ae/A up to 70 days prior to harvest. IR-4 has requested uses for dry beans and snap beans at a maximum seasonal rate of 0.375 lb ae/A up to 30 days prior to harvest. HED notes that the residue data submitted for dry beans does not support the requested PHI, but rather supports a PHI of 45 days. Further, adequate data are not available to support the requested rotational crop restrictions.

Registered products referenced in this action that include fomesafen sodium as the active ingredient include a 2 lb ae/gal SC/L formulation known as Reflex® Herbicide for use on soybeans and a 1.88 lb ae/gal SC/L formulation known as Flexstar®, also for use on soybeans.

The toxicological database for fomesafen is considered complete and adequate for the purposes of this risk assessment. Fomesafen has a low order of acute toxicity by the oral route of exposure (Toxicity Category III), is severely irritating to the eye and is moderately irritating to the skin. In the subchronic and chronic toxicity study in rats and mice, food consumption or food efficiency, body weight/body weight gain and histopathological changes in the liver were the parameters that were most often affected. In addition, dogs and mice also showed hematological changes (e.g., decreased erythrocyte count, hemoglobin, or hematocrit). Carcinogenicity was not observed in the rat chronic toxicity/carcinogenicity study. Liver tumors were produced in the mouse carcinogenicity study; however, HED's Cancer Assessment Review Committee (CARC) determined that fomesafen should be classified as "Not Likely to be Carcinogenic to Humans". This decision was based on the weight-of-evidence which supports activation of peroxisome proliferator-activated receptor alpha (PPARα) as the mode of action for fomesafen-induced hepatocarcinogenesis in mice. Fomesafen was not considered to be mutagenic, nor did this chemical produce neurotoxic effects. No quantitative or qualitative evidence of increased susceptibility was seen following *in utero* exposure to rats or rabbits in developmental studies or in the reproduction study.

There were no observed toxic effects which were attributable to a single dose of fomesafen; therefore, an endpoint for acute dietary risk was not selected. The endpoint and doses used to establish the chronic reference dose (RfD) were taken from the combined chronic toxicity/carcinogenicity study in rats and reflected the lowest endpoint in the database for liver effects. At the LOAEL of 5 mg/kg/day effects seen were hyalinization of the liver in male rats,

the NOAEL for this effect was 0.25 mg/kg/day. The cRfD of 0.0025 mg/kg/day was based on the study NOAEL with application of the standard uncertainty factor of 100x for inter- and intra-species variabilities. The special FQPA safety factor was reduced to 1X given the lack of evidence of increased susceptibility; therefore, the cPAD is 0.0025 mg/kg/day and is used for the chronic dietary exposure assessment.

An endpoint relevant to incidental oral exposure (short and intermediate term) for the population of concern (infants and children) was selected from the 90-day rat feeding study. The NOAEL from the study is 0.5 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 seen at the LOAEL of 10 mg/kg/day. The recommended minimum MOE for this assessment is 100 based on the standard 100X uncertainty factor for inter- and intra-species variability and reflecting a special FQPA SF of 1X.

Endpoints and doses to assess short- and intermediate-term dermal risk were selected from the prenatal developmental toxicity study in the rat. An endpoint from an oral study was selected since the endpoints and doses selected from the 21-day dermal toxicity study in rats would not be protective of the post implantation loss seen in the developmental toxicity study in rats. The NOAEL is 100 mg/kg/day, based on postimplantation loss and significantly decreased maternal body weight gain seen at the LOAEL of 200 mg/kg/day. The recommended minimum MOE for this assessment was 100 based on the standard uncertainty factor of 100X for inter- and intra-species variabilities. A dermal absorption value of 20% (based on dermal absorption factors for similarly structured compounds) was applied during the conduct of the short- and intermediate-term dermal risk assessments. An endpoint and doses to assess long-term dermal risk were selected from the combined chronic toxicity/carcinogenicity rat study. An endpoint from an oral study was selected since the endpoints and doses selected from the 21-day dermal toxicity study in rats would not be protective of the post implantation loss seen in the developmental toxicity study in rats. The NOAEL is 0.25 mg/kg/day, based on hyalinization of the liver in males seen at the LOAEL of 5 mg/kg/day. Based on the selection of an oral endpoint, if a long-term dermal risk assessment had been appropriate, a dermal absorption value of 20% would have been applied.

An inhalation study was not available, therefore endpoints and doses to assess inhalation risk from short-, intermediate- and long-term exposure were all selected from oral studies. Short- and intermediate term selections were established from the 90-day rat feeding study. The NOAEL is 0.5 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 seen at the LOAEL of 10 mg/kg/day. The endpoint for the long-term inhalation risk assessment was selected from the combined chronic toxicity/carcinogenicity study in rats. The NOAEL is 0.25 mg/kg/day, based on hyalinization of the liver in males seen at the LOAEL of 5 mg/kg/day. For all three duration risk assessments, a minimum MOE of 100 is recommended based on application of the standards 100X uncertainty factor to inter- and intra-species variability.

The CARC has classified fomesafen as “Not Likely to be Carcinogenic to Humans”.

For the purposes of this risk assessment only, the nature of the residue in plants has been adequately delineated. The residue of concern in soybean seed, dry beans, snap beans and cotton is fomesafen *per se*. Further, HED concludes that the proposed/registered uses of fomesafen on cotton, dry and snap beans, and soybeans result in a 40 CFR §180.6(a)(3) situation for livestock commodities; i.e., there is no reasonable expectation of finite residues in livestock commodities and tolerances are not needed.

Data are required depicting the stability of residues of fomesafen in/on the following commodities: cotton gin byproducts stored frozen for up to 11 months; soybean hulls and oil stored frozen for up to 10 months; corn cob stored frozen for up to 7 months; wheat forage and straw during frozen storage for up to 13 months; and field corn or sorghum forage and stover during frozen storage for up to 10 months. Adequate storage stability data are available for all other commodities that are the subject of this action. Adequate crop field trial data have been submitted for dry bean, snap bean, soybean and cotton, provided deficiencies noted in the cotton field trial data are addressed. For all commodities, the data reflect the maximum rates and minimum PHIs requested and have sufficient geographic representation to support full U.S. registrations for soybeans, cotton, dry beans and snap beans. All crop field trial studies are supported by adequate storage stability data. The soybean crop field trial data indicate that a tolerance for soybean aspirated grain fractions is needed. Adequate processing data have been submitted for cotton and soybean which indicate that quantifiable residues of fomesafen are not likely in the processed commodities of cotton and soybean. There are adequate analytical methods to enforce the recommended tolerances. The existing confined rotational crop data are not adequate; therefore, the Reflex® Herbicide label should be amended to permit immediate replanting of soybeans, cotton, dry beans and snap beans only with a restriction that other crops can only be planted 12 months after treatment or 18 months after treatment if based on phytotoxicity concerns.

U.S. tolerances are currently established for residues of fomesafen in/on soybeans at 0.05 ppm. No Codex 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, and a Mexican MRL of 0.05 mg/kg has been established for residues of fomesafen in/on soybeans.

The environmental fate data indicated that fomesafen is likely to be persistent and mobile in aquatic and terrestrial environments. EFED has calculated estimated environmental concentrations in surface water using PRZM-EXAMS modeling and has recommended the use of a prospective groundwater water study to estimate concentrations in drinking water derived from groundwater sources. Since the only dietary assessment relevant to this action is a chronic dietary assessment, HED used the maximum annual average concentration value from PRZM-EXAMS of 10.5 µg/L for surface water EECs and used the prospective groundwater monitoring concentration of 1.0 µg/L to estimate exposure in drinking water likely to result from residues in groundwater.

Acute dietary risk assessments were not required as there were no endpoints identified attributable to a single exposure of fomesafen. Additionally, aggregate acute risk assessments were not required.

There are no residential uses for products formulated with fomesafen sodium, therefore an incidental oral exposure and risk assessment (short and intermediate term) was not required. Further, short-/intermediate- and long-term dermal and inhalation risk assessments were not required for residential exposures. Based on the lack of a relevant exposure scenario, short- and intermediate-term aggregate risk assessments are not required.

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 PAD. An additional DEEM-FCID™ analysis was conducted in which the estimated drinking water concentrations (EDWCs) from the Environmental Fate and Effects Division were included directly into the assessment. 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 chronic population adjusted dose (cPAD); and the exposure for food plus ground water was 0.000107 mg/kg/day, which utilized 4.3% of the cPAD. For this same group, "all infants" the food only exposure was 0.000038 mg/kg/day, which utilized 1.5% of the cPAD. Since there are no residential uses for fomesafen, the chronic aggregate risk assessment would combine food and water only. As the chronic dietary risk assessment was conducted with the direct inclusion of water into the analysis, the chronic dietary (food and water) risk assessment is also the chronic aggregate risk assessment.

The Cancer Assessment Review Committee (CARC) classified fomesafen as "not likely to be carcinogenic to humans"; therefore, a cancer risk assessment was not required.

There is potential for occupational exposure to fomesafen during mixing, loading, application, and postapplication activities; therefore, short- and intermediate-term work exposure and risk assessments were conducted to support this Section 3 registration. Fomesafen is typically applied early in the growing season and chronic occupational exposures to fomesafen would not be expected to occur. The Margin of Exposure (MOE) for determining the level of concern (LOC) for occupational populations is 100, which includes the standard safety factors of 10X for intraspecies variability (i.e. differences among humans) and 10X for interspecies variability (differences between humans and animals). When the MOE is greater than 100, the risks are not of concern. The MOEs for occupational exposures were calculated for short/intermediate term dermal and inhalation exposures. These MOEs were calculated separately because the dermal and inhalation endpoints were based upon different effects. Standard assumptions, PHED unit exposure data and maximum label rates were used.

Most occupational scenarios did not result in risks of concern, with the exception of inhalation risks to aerial applicators. Inhalation MOEs for the mixer/loader scenarios for aerial application were of concern with baseline PPE. PF5 respirators are required to achieve acceptable MOEs (i.e., greater than the target MOE of 100). All of the dermal MOEs exceed the target MOE of

100 with single layer PPE (includes long-sleeve shirt, long pants, gloves) 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.

EPA has not made a common mechanism of toxicity finding as to fomesafen and any other substances, and fomesafen does not appear to produce a toxic metabolite produced by other substances. As a result, for the purposes of this tolerance action, EPA has not assumed that fomesafen has a common mechanism of toxicity with other substances.

HED concludes that provided deficiencies identified in Section 10.0 of this risk assessment are satisfied as a condition of registration, the available toxicity, residue chemistry and occupational/residential data along with this risk assessment, support the registrant's request to add a post-bloom use on soybeans and reduce the current tolerance on soybean seed. Additionally, the available data support the Section 3 registration and establishment of tolerances for the use of fomesafen on cotton, dry beans and snap beans. The available data, however, do not support the 30-day PHI requested for dry beans, but do support a 45-day PHI for that commodity. Further, the data do not support the rotational crop restrictions on the proposed Reflex® Herbicide label; therefore the label must be amended to permit rotation only to those crops that are the subject of this action. Additionally, the field trial data indicate that in addition to the requested tolerances, a tolerance is required for aspirated grain fractions as a result of the proposed use on soybeans. Finally, HED notes that while the label for Reflex® Herbicide limits application of fomesafen to the Eastern United States, the residue data submitted are of sufficient geographic representation to support a full U.S. registration; therefore, recommendations for tolerances and this risk assessment reflect uses for the subject crops based on a full U.S. registration.

2.0 Ingredient Profile

Fomesafen (5-[2-chloro-4-(trifluoromethyl)phenoxy]-N-(methylsulfonyl)-2-nitrobenzamide) is a selective herbicide which may be applied preplant, preemergence, and/or postemergence for control and suppression of broadleaf weeds, grasses, and sedges. Fomesafen is currently registered for preplant, preemergence and early postemergence use on soybeans. This action proposes to add later season uses for soybeans and preplant, preemergence and/or postemergence uses for cotton, dry beans and soybeans. There are no residential uses of fomesafen. The existing labels allow ground and aerial application, and do not allow chemigation. The current label for Reflex® Herbicide, the sole label proposed for amendment in this action, specifies a 24-hr reentry interval for workers. Fomesafen products are formulated as the sodium salt and the concentration of the active ingredient in the formulation is expressed in terms of the acid equivalent (ae). Fomesafen sodium is in the diphenylether chemical class and it mode of action is via inhibition of protoporphyrinogen oxidase (PPO) in the plant.

Registered products referenced in this action which include fomesafen sodium as the active ingredient include a 2 lb ae/gal SC/L formulation known as Reflex® Herbicide for use on soybeans and a 1.88 lb ae/gal SC/L formulation known as Flexstar®, also for use on soybeans.

2.1 Summary of Registered/Proposed Uses

TABLE 2.1. Summary of Directions for Use of Fomesafen Sodium.						
Trade Name	Applic. Timing, Type, and Equip.	Applic. Rate (lb ae/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ae/A)	PHI (days)	Use Directions and Limitations
Cotton						
Reflex® Herbicide (Label booklet SCP 993A-L1 0502B)	Preemergence Broadcast or banded Ground	0.25 - 0.375	Not specified (NS)	0.1875 in alternate years - 0.375 each year[1]	NS	Apply preemergence as a broadcast or banded treatment only to coarse soils. Do not apply as a preemergence treatment to medium or fine-textured soils as crop injury will likely occur.
	Postemergence Post-directed, hooded, or shielded Ground	0.25 - 0.375	NS	0.1875 in alternate years - 0.375 each year[1]	70	Apply in emerged cotton as a post-directed treatment. Apply when cotton is at least 6" tall with less than 4" of brown bark by post-directed application. Use only hooded or shielded spray equipment in cotton that is 6" to 12" in height. For layby applications, make a post-directed application to the base of the cotton plant, avoiding contact with any non-barked portion of the cotton plant or foliage
	Preplant Spot treatment incorporated Ground	0.375	12	0.375	NS	**Use is for Texas only to control lakeweed.** Apply using precision post-directed, hooded or shielded application equipment, do not apply over the top of cotton or allow to contact cotton foliage. Cotton should be 6" high before applying. When cotton is 6 – 11" spray should contact no more than bottom 2 – 3" of the stalk. When cotton is $\geq$ 12" spray should contact no more than the bottom third of the cotton stalk. Do not use liquid nitrogen on cotton.
Dry beans						
Reflex® Herbicide (Label booklet SCP 993A-L1 0502B)	Postemergence Broadcast Ground or aerial	NS	2	0.1875 in alternate years - 0.375 each year[1]	30	Application is to be made with a spray adjuvant (see "General use directions" below) when beans have at least 4 fully expanded trifoliate leaves. Use of a nitrogen adjuvant is prohibited. Grazing green forage or stubble is prohibited. Use of hay or straw for feed or bedding is prohibited.
Snap beans						

TABLE 2.1. Summary of Directions for Use of Fomesafen Sodium.						
Trade Name	Applic. Timing, Type, and Equip.	Applic. Rate (lb ae/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ae/A)	PHI (days)	Use Directions and Limitations
Reflex® Herbicide (Label booklet SCP 993A-L1 0502B)	Postemergence Broadcast Ground or aerial	NS	2	0.1875 in alternate years - 0.375 each year[1]	30	Application is to be made with a spray adjuvant (see "General use directions" below) when beans have at least 1 fully expanded trifoliate leaf. Use of a nitrogen adjuvant is prohibited. Grazing treated areas or harvesting for forage or hay is prohibited. Use of hay or straw for feed or bedding is prohibited.
Soybean						
Reflex® Herbicide (Label booklet SCP 993A-L1 0502B)	Preplant surface or preemergence Broadcast Ground	NS	NS	0.1875 - 0.25 in alternate years[1]	NS	Applications may be made in Regions 1 - 4.
	Postemergence Broadcast Ground or aerial	NS	NS	0.1875 in alternate years - 0.375 each year[1]	45	Applications may be made in Regions 1-5.

[1] The label booklet specifies five use regions with specific seasonal maximum application rates. The rates range with the label use Region 1 having the highest seasonal application rate reflects application at 0.375 lb ae/A each year and label use Region 5 with the lowest seasonal application rate reflects application of up to 0.1875 lb ae/A in **alternate years**. Details of the seasonal maximums for all label use Regions are presented below under "General Use Directions"

[2] If applications are made in 2 consecutive years, a 2-year interval should be allowed before another application.

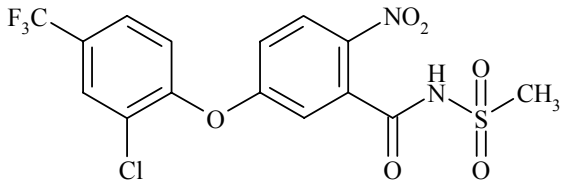
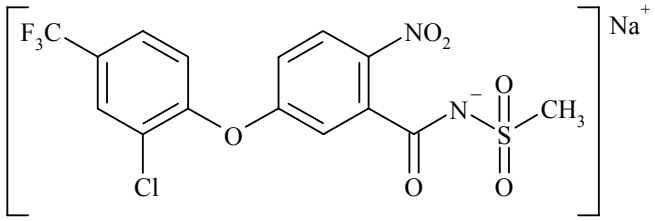
General use directions

The label booklet specifies that use is restricted to the eastern half of the U.S. with the following boundaries: ND, SD, KS, and NE, all counties east of and/or intersected by U.S. Rt. 281 (corresponding to the westernmost boundary of EPA Region 5); OK east of U.S. Rt. 75 and east of Indian Nation Parkway; and TX east of U.S. Rt. 77 to state Rt. 239 including all of Calhoun County. The area is subdivided into the following five use regions:

Region 1: AL, AR, GA, LA, MS, NC, SC, and TN, and sections of MO, OK, and TX
Region 2: DE, KY, MD, VA, WV, and sections of IL, IN, OH, and PA
Region 3: CT, IA, MA, ME, NH, NJ, NY, RI, VT, and WI, and sections of IN, IL, MO, OH,
and PA
Region 4: Sections of KS, MI, MN, ND, NE, SD, and WI
Region 5: Sections of ND, SD, and MN

Maximum yearly or biannual rates are restricted by label regions as follows: 0.375 lb ae/A/year in Region 1; 0.375 lb ae/A in alternate years in Region 2; 0.313 lb ae/A in alternate years in Region 3; 0.25 lb ae/A in alternate years in Region 4; and 0.1875 lb ae/A in alternate years in Region 5.

2.2 Structure and Nomenclature

Table 2.2 Fomesafen and its Sodium Salt Nomenclature	
Chemical structure	
Common name	Fomesafen
Molecular formula	$C_{15}H_{10}ClF_3N_2O_6S$
Molecular weight	438.77
PC Code	N/A
IUPAC name	5-(2-chloro-α,α,α-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	$C_{15}H_9ClF_3NaN_2O_6S$
Molecular weight	460.75
PC Code	123802
IUPAC name	5-(2-chloro-α,α,α-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

2.3 Physical and Chemical Properties

TABLE 2.3. Physicochemical Properties of Fomesafen		
Parameter	Value	Reference
Melting point	220-221 °C	HED Memo, 9/3/82, W. Anthony
pH	8.2 (94% TGAI)	CSF (EPA Reg. No. 100-1017; 10/13/00)
Density, bulk density, or specific gravity	1.28 g/cm^3 at 20 °C	HED Memo, 9/10/86, C. Trichilo
Water solubility at 25 °C	600 g/L at pH 7 <10 ppm at pH 1-2 50 mg/L	HED Memo, 9/3/82, W. Anthony HED Memo, 9/10/86, C. Trichilo

TABLE 2.3. Physicochemical Properties of Fomesafen		
Parameter	Value	Reference
Solvent solubility	g/L Acetone 300 Cyclohexanone 150 Methanol 25 Hexane 0.5 Xylene 1.9	HED Memo, 9/10/86, C. Trichilo
Vapor pressure	$<7.5 \times 10^{-7}$ mmHg at 50 °C	The Pesticide Manual [1]
Dissociation constant, pK_a	2.7 at 20 °C	
Octanol/water partition coefficient	Log K_{OW} = 2.9 at pH 1	
UV/visible absorption spectrum	Not available	

[1] The Pesticide Manual; A World Compendium, The British Crop Protection Council (toxnet.nlm.nih.gov)

3.0 Metabolism Assessment

3.1 Comparative Metabolic Profile

Fomesafen is readily absorbed in male and female rats after oral dosing, but there are differences in excretion patterns when rat receive low oral doses. The major route of elimination in females is in the urine whereas in males, it is in the feces. These differences can also be accounted for by biliary excretion. The sex difference is not evident at higher doses where the urine is the main route of excretion for both sexes. Some enterohepatic recirculation is evident. At higher doses, the vast majority is excreted unchanged, but at lower doses a lesser amount (60%) is excreted unchanged. The major metabolite (10%) is 5 - (2 - chloro - α, α, α - trifluoro - tolyloxy) - anthranilic acid. The greatest concentration of the parent and/or metabolites is present in the liver, kidney, intestinal contents, and stomach. Radioactivity was also detected in the blood, lungs, eyes and CNS, with only trace amounts being detected in other tissues. After 5 days, radioactivity was only detected in the liver and kidneys. Part, or all, of the phenoxy anthranilic metabolite may be due to action by intestinal microorganisms. The rat has a very limited capacity to metabolize fomesafen.

Beagles received a low oral dose of fomesafen. Peak blood levels occurred within 3 hours, then rapidly declined. Excretion in both sexes was predominantly in urine and to a lesser extent in the feces. Most of the fomesafen (96%) was excreted within 24 hours in both sexes. Radioactivity in the tissues at 96 hours was low, with the highest levels in the liver (0.54% of the dose). Fomesafen was not extensively metabolized in the dog and was recovered to a large extent unchanged.

Similar to the rat and beagle, in both goat and poultry metabolism studies, it does not appear that fomesafen is extensively metabolized. The backbone structure of the molecule appears to remain intact with the major metabolic pathway involving reduction of the parent nitro group to an amino group yielding the metabolite, 5-(2-chloro-α,α,α-trifluoro-p-tolyloxy)-N-methylsulfonylanthranilamide, followed by subsequent hydrolysis of the methylsulfonylamide group to the carboxylic acid producing the same metabolite identified in the rat metabolism study, 5-(2-chloro-α,α,α-trifluoro-p-tolyloxy) anthranilic acid. In the goat metabolism study, 47% of the radioactivity was excreted and the highest residues were found in liver and kidney

with very low levels of residue found in other tissues and milk. In the poultry metabolism study, 95 - 99% of the residue was excreted and the highest residues were found in liver, muscle and fat, with very low levels of residue being found in eggs.

In contrast, in soybeans, fomesafen appears to be extensively metabolized. Studies with soybeans suggest that fomesafen is absorbed, translocated, and rapidly and extensively metabolized. The parent molecule was cleaved at the ether linkage between the two rings. In soybeans, the resulting trifluoromethyl-chlorophenol was found to form conjugates with plant components, which were further metabolized to unidentified water-soluble fragments. The nitrophenol portion of the parent molecule conjugated with cysteine, and the conjugate was further metabolized to unidentified water-soluble fragments. Only trace amounts of the parent were found to be present in plant commodities at harvest. There was some evidence of incorporation or radioactivity into naturally-occurring plant components. In cotton, fomesafen is also fairly extensively metabolized. Very low levels of radioactivity were found in cotton seed. In gin byproducts, parent compound was found in quantities ranging from 6 - 28% of the TRR in the gin byproducts. Only one other metabolite, 1-[2-chloro-4-(trifluoromethyl)phenyl]-β-D-glucopyranoside, was found in significant quantities. The registrant has proposed that fomesafen is metabolized in cotton via hydrolysis of the biphenyl ether linkage, which would yield 2-chloro-4-(trifluoromethyl)phenol. This compound is then conjugated with uridine diphosphate glucose to form 1-[2-chloro-4-(trifluoromethyl)phenyl]-β-D-glucopyranoside. Metabolite D would then be formed via sulfate transfer from 3'-phosphoadenylsulfate to the C-6 position of glucose, also yielding adenosine-3',5'-biphosphate.

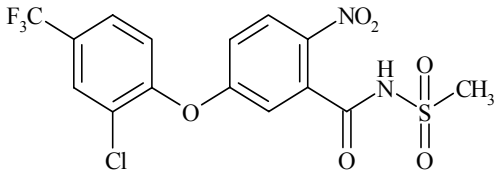
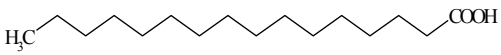
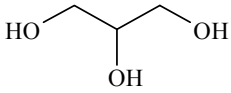
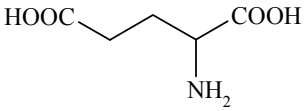
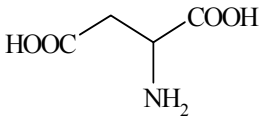
Details of the plant and livestock metabolism studies, as well as tables of the structures of identified metabolites are contained in Section 3.2, below.

3.2 Nature of the Residue in Foods

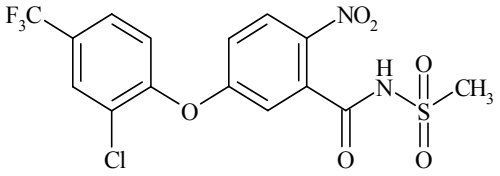
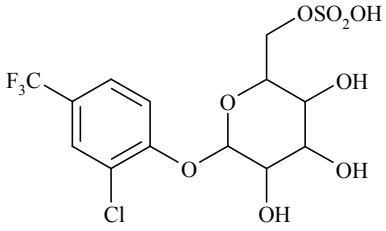
3.2.1 Description of Primary Crop Metabolism

Several metabolism studies with soybeans were reviewed in conjunction with a temporary tolerance petition (PP#2G2745). Studies with soybeans indicated that fomesafen is absorbed, translocated, and rapidly and extensively metabolized. The parent molecule was cleaved at the ether linkage between the two rings. The resulting trifluoromethyl-chlorophenol was found to form conjugates with plant components, which were further metabolized to unidentified water-soluble fragments. The nitrophenol portion of the parent molecule conjugated with cysteine, and the conjugate was further metabolized to unidentified water-soluble fragments. Only trace amounts of the parent were found to be present in plant commodities at harvest. There was some evidence of incorporation or radioactivity into naturally-occurring plant components.

TABLE 3.2.1.1 Structures of Identified Compounds from the Soybean Metabolism Study

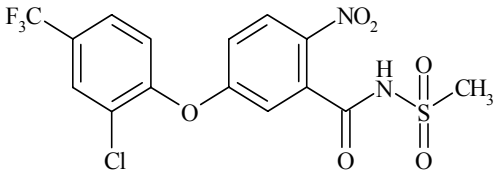
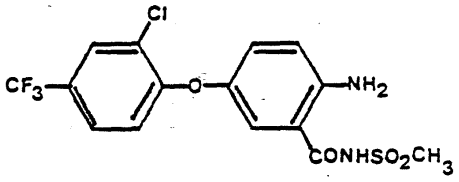
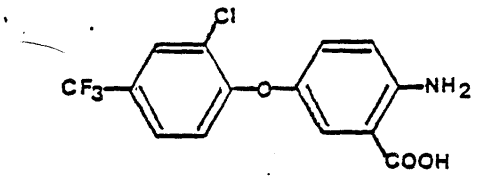
Common name/code Figure C.3.1 ID No.	Chemical name	Chemical structure
Fomesafen	5-(2-chloro-α,α,α-trifluoro-p-tolyloxy)-*N*-methyl sulfonyl-2-nitrobenzamide	
Palmitic acid		
Glycerol		
Glutamic acid		
Aspartic acid		

Based on the results of the cotton metabolism study, the registrant has proposed that fomesafen is metabolized in cotton via hydrolysis of the biphenyl ether linkage, which would yield 2-chloro-4-(trifluoromethyl)phenol. This compound is then conjugated with uridine diphosphate glucose to form 1-[2-chloro-4-(trifluoromethyl)phenyl]-β-D-glucopyranoside. Metabolite D (shown in Table 3.2.1.2, below) would then be formed via sulfate transfer from 3'-phosphoadenylsulfate to the C-6 position of glucose, also yielding adenosine-3',5'-biphosphate.

TABLE 3.2.1.2 Structures of Identified Compounds from the Cotton Metabolism Study		
Common name/code Figure C.3.1 ID No.	Chemical name	Chemical structure
Fomesafen	5-(2-chloro-α,α,α-trifluoro-p-tolyloxy)-*N*-methyl sulfonyl-2-nitrobenzamide	
Metabolite D	1-[2-chloro-4-(trifluoromethyl)phenyl]-β-D-glucopyranoside	

3.2.2 Description of Livestock Metabolism

Both goat and poultry metabolism studies were conducted to investigate the potential for residues of fomesafen or its metabolites to be present in meat, milk, poultry or eggs. In the goat metabolism study, 47% of the radioactivity was excreted. At highly exaggerated dosing levels (515x the maximum theoretical dietary burden to beef and dairy cattle and 690x the maximum theoretical dietary burden to swine) in the goat metabolism study, residues of fomesafen were not found in milk, tissue or excreta. TRR in tissues were 0.2 ppm in liver, 0.28 ppm in kidney, 0.009 ppm in meat, 0.06 ppm in fat and 0.014 ppm in milk. The identified metabolites were 5-(2-chloro-α,α,α-trifluoro-p-tolyloxy)-N-methylsulfonylanthranilamide (compound XV) and 5-(2-chloro-α,α,α-trifluoro-p-tolyloxy) anthranilic acid (compound V). Compound XV was found at 10% TRR in liver and 20.9% TRR in kidney, and compound V was found at 34.5% TRR in liver and 33.9% TRR in kidney. In the poultry metabolism study, reflecting highly exaggerated dosing rates (~1300x the maximum theoretical dietary burden to poultry. TRR were 0.001-0.011 ppm in egg white, 0.0003-0.123 ppm in egg yolk, 0.19-0.40 ppm in liver, 0.010-0.034 ppm in muscle, and 0.030-0.048 ppm in fat. Approximately 95-99% of the dosed radioactivity was excreted. Fomesafen was found to be the major residue in eggs (>50% TRR) and liver (>70% TRR). Compounds V and XV were found in eggs (<25% TRR) and compound V was found in liver (~15% TRR). The nature of the residue in livestock has been adequately delineated and for the purpose of this action, the significant components of the animal (goats and poultry) residues which were found in highly exaggerated rate studies were fomesafen and its metabolites 5-(2-chloro-α,α,α-trifluoro-p-tolyloxy) anthranilic acid and 5-(2-chloro-α,α,α-trifluoro-p-tolyloxy)-N-methylsulfonylanthranilamide. HED further notes that the proposed/registered uses of fomesafen on soybeans, cotton, dry beans and snap beans result in a 40 CFR §180.6(a)(3) situation for livestock commodities; i.e., there is no reasonable expectation of finite residues in livestock commodities and tolerances are not needed.

TABLE 3.2.2.1 Structures of Identified Compounds from the Livestock Metabolism Studies		
Common name/code Figure C.3.1 ID No.	Chemical name	Chemical structure
Fomesafen	5-(2-chloro-α,α,α-trifluoro-p-tolyloxy)-*N*-methyl sulfonyl-2-nitrobenzamide	
Compound XV	5-(2-chloro-α,α,α-trifluoro-p-tolyloxy)-N-methylsulfonylanthranilamide	
Compound V	5-(2-chloro-α,α,α-trifluoro-p-tolyloxy) anthranilic acid	

HED notes that the animal metabolite, 5-(2-chloro-α,α,α-trifluoro-p-tolyloxy) anthranilic acid (compound V) is a regulated metabolite of the pesticide, acifluorfen. Given that this metabolite has been found in controlled fomesafen animal metabolism studies at very high doses, and HED has concluded that for the purpose of this registration action, there is no reasonable expectation of finite residues of parent fomesafen or its metabolites in livestock commodities, no further assessment is required to support this Section 3 action. However, should future new registration actions result in the likelihood of measurable residues in animal commodities, an aggregate risk assessment for this metabolite may be required.

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

The registrant has submitted both a confined rotational crop study and rotational crop field trials and has requested rotation to crops other than the primary crops that are the subject of this action. HED has reviewed the data and concluded that the confined rotational crop study is not adequate to support decisions relevant to rotational crop issues at this time, nor is it sufficient to understand the nature of the residue in rotated crops. A new confined rotational crop study will be required; therefore, the registrant has been requested to revise the label that to permit immediate replanting of soybeans, cotton, dry beans and snap beans only with a restriction that other crops can only be planted 12 months after treatment or 18 months after treatment if based

on phytotoxicity concerns.

3.3 Environmental Degradation

EFED has reviewed the available environmental fate data in their document entitled *Tier II Drinking Water Assessment for Fomesafen use on cotton, soybeans, dry beans, and snap beans* (memorandum dated 9/27/05 from James Hetrick to Daniel Rosenblatt; D314014, D354673, D318123). Fomesafen was found to have a high water solubility and a low vapor pressure. In the hydrolysis study, fomesafen was found to be stable at pH7, and in the photolysis study, fomesafen had a half-life of 289 days in pH 7 buffer solution. In the aerobic soil metabolism study, the upper 90th percentile mean half-life was 429 days. In the aerobic aquatic metabolism study, the upper 90th percentile mean half-life was 116 days and the compound was assumed to be stable upon evaluation of the aquatic metabolism anaerobic half-life. The EFED reviewer concluded that, based on the environmental fate data, fomesafen should be very mobile and highly persistent in terrestrial and aquatic environments.

3.4 Toxicity Profile of Major Metabolites and Degradates

As noted previously, fomesafen is extensively metabolized in plant matrices. Based on the metabolism profile, HED did not identify major metabolites or degradates that were expected to be of toxicological concern or were likely to be significantly more toxic than the parent compound.

Based on the results of animal metabolism studies conducted at highly exaggerated rates, HED has concluded that there is no reasonable expectation of finite residues of fomesafen in livestock commodities based on the registration of the pesticide for use on soybeans, cotton, dry beans and snap beans.

3.5 Summary of Residues for Tolerance Expression and Risk Assessment

3.5.1 Tabular Summary

Table 3.5. Summary of Metabolites and Degradates to be Included in the Risk Assessment and Tolerance Expression

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	Parent Fomesafen	Parent Fomesafen
	Rotational Crop	Unknown[1]	Unknown[1]
Livestock	Ruminant	N/A[2]	N/A[2]
	Poultry	N/A[2]	N/A[2]
Drinking Water		Parent Fomesafen	N/A

[1] The nature of the residue in rotational crops has not been adequately delineated. For this action rotation is limited only to the primary crops that are the subject of this action.

[2] HED has determined that use of fomesafen on the primary crops that are the subject of this action will not likely result in detectable residues in livestock commodities (180.6 (a)(3)).

3.5.2 Rationale for Inclusion of Metabolites and Degradates

Based on the results of the plant metabolism studies submitted, residues of concern in soybeans, cotton, dry beans and snap beans are parent compound, fomesafen *per se*. There were no additional major metabolites that were either found to be of toxicological concern, or were likely to be significantly more toxic than the parent compound; therefore, no additional metabolites or degradates were included in either the risk assessment or the tolerance expression.

Based on the results of animal metabolism studies conducted at highly exaggerated rates, HED has concluded that there is no reasonable expectation of finite residues of fomesafen in livestock commodities based on the existing and proposed registration of the pesticide for use on soybeans, cotton, dry beans and snap beans.

4.0 Hazard Characterization/Assessment

The toxicological database for fomesafen is considered adequate for hazard characterization.

4.1 Hazard Characterization

Fomesafen has a low order of acute toxicity by the oral route of exposure (Toxicity Category III). Fomesafen is severely irritating to the eye and is moderately irritating to the skin. In the subchronic and chronic toxicity studies in rats and mice food consumption or food efficiency, body weight and body weight gain and histopathological changes in the liver were parameters that were most often affected. In addition, dogs and mice also showed hematological changes (e.g., decreased erythrocyte count, hemoglobin, or hematocrit). Carcinogenicity was not observed in the rat chronic toxicity/carcinogenicity study. Liver tumors were produced in the mouse carcinogenicity study; however, HED's Cancer Assessment Review Committee (CARC) determined that fomesafen should be classified as "Not Likely to be Carcinogenic to Humans" (HED Doc No. 0053835). This decision was based on the weight-of-evidence which supports activation of peroxisome proliferator-activated receptor alpha (PPARα) as the mode of action for fomesafen-induced hepatocarcinogenesis in mice. Fomesafen was not considered to be mutagenic (HED Doc No. 0053835).

No quantitative or qualitative evidence of increased susceptibility was seen following *in utero* exposure to rats or rabbits in developmental studies or in the reproduction study.

Fomesafen is readily absorbed in male and female rats after oral dosing, but there are differences in excretion patterns when rat receive low oral doses. The major route of elimination in females is in the urine whereas in males, it is in the feces. These differences can also be accounted for by biliary excretion. The sex difference is not evident at higher doses where the urine is the main route of excretion for both sexes. Some enterohepatic recirculation is evident. At higher doses, the vast majority is excreted unchanged, but at lower doses a lesser amount (60%) is excreted

unchanged. The major metabolite (10%) is 5 - (2 - chloro - α, α, α - trifluoro - tolyloxy) - anthranilic acid. The greatest concentration of the parent and/or metabolites is present in the liver, kidney, intestinal contents, and stomach. Radioactivity was also detected in the blood, lungs, eyes and CNS, with only trace amounts being detected in other tissues. After 5 days, radioactivity was only detected in the liver and kidneys. Part, or all, of the phenoxy anthranilic metabolite may be due to action by intestinal microorganisms. The rat has a very limited capacity to metabolize fomesafen.

Beagles received a low oral dose of fomesafen. Peak blood levels occurred within 3 hours, then rapidly declined. Excretion in both sexes was predominantly in urine and to a lesser extent in the feces. Most of the fomesafen (96%) was excreted within 24 hours in both sexes. Radioactivity in the tissues at 96 hours was low, with the highest levels in the liver (0.54% of the dose). Fomesafen was not extensively metabolized in the dog and was recovered to a large extent unchanged.

Table 4.1a: Acute Toxicity Profile - Fomesafen

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral	00247589	LD_{50} =1250-2000 mg/kg	III
81-2	Acute Dermal	-	-	-
81-3	Acute Inhalation	-	-	-
81-4	Primary Eye Irritation	00247589	severe irritation	-
81-5	Primary Skin Irritation	00247589	moderate irritation	-
81-6	Dermal Sensitization	-	-	-

Table 4.1b Subchronic, Chronic and Other Toxicity Profile - Fomesafen

Table 4.1b Subchronic, Chronic and Other Toxicity Profile - Fomesafen		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3050 28-Day mice - diet	40786709 (1980) Acceptable/Non-Guideline 0, 5, 15, 50, 150, 500, 1500 or 1500 ppm (0/0, 0.71/0.94, 2.13/2.87, 7.20/8.30, 20.7/27.1, 68.9/83.4, 209.1/246.8, or 917.2/1247.6 mg/kg/day) [M/F]	NOAEL = 1500 ppm (209/247 mg/kg/day) LOAEL = 5000 ppm (917/1247 mg/kg/day in M/F) based on decreased body weights and body weight gains, decreased food efficiency, hematology (decreased erythrocyte count, hemoglobin, mean corpuscular volume, and mean corpuscular hemoglobin), bile duct hyperplasia, decreased uterine size in females, and decreased size of the seminal vesicles in males
870.3100 90-Day rats - diet	00103013 (1981) Acceptable/Guideline 0, 1, 5, 100 or 1000 ppm (0, 0.1, 0.5, 10 and 100 mg/kg/day)	NOAEL = 5 ppm (0.5 mg/kg/day) LOAEL =100 ppm (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
870.3150 26-Week dogs - diet	00103014 (1981) Acceptable/Guideline 0, 0.1, 1.0 or 25 mg/kg/day	NOAEL = 1.0 mg/kg/day LOAEL = 25 mg/kg/day based on hematology (decreased hemoglobin and hematocrit concentrations and erythrocyte count and increased platelet count and prothrombin time)
870.3200 21-Day dermal - rabbit	00135632 (1983) Acceptable/Guideline 0, 10, 100 or 1000 mg/kg	NOAEL = 1000 mg/kg/day LOAEL was not observed
870.3700 Prenatal developmental toxicity - rabbit	00109214 (1981) Unacceptable/Guideline 0, 2.5, 10 or 40 mg/kg/day	Maternal/Developmental NOAELs and LOAELs were unable to be determined due to the occurrence of an apparent bacterial infection in the animal colony
870.3700 Prenatal developmental toxicity - rat	00164903 (1981) Acceptable/Guideline 0, 50, 100 or 200 mg/kg/day	[This study was considered with: 1) Report Nos. CTL/P/656 and CTL/P/656S, MRID #001013016, and 2) information provided by Syngenta in their submission (DP 316263, MRID 46527208) in establishing the NOAEL and LOAEL. With the additional information, the following conclusions were made.] Maternal NOAEL = 100 mg/kg/day Maternal LOAEL = 200 mg/kg/day based on staining of the ventral fur and significantly decreased body weight gain (>10%) Developmental NOAEL = 100 mg/kg bw/day Developmental LOAEL = 200 mg/kg bw/day based on postimplantation loss observed in study CTL/P/576 (MRID 00164903)

Table 4.1b Subchronic, Chronic and Other Toxicity Profile - Fomesafen		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3700 Prenatal developmental toxicity - rat	**00103016 (1982) Acceptable/Guideline 0, 1.0, 7.5 or 50 mg/kg/day**	**[The maternal and developmental toxicity LOAEL and NOAEL were not established in this study. However, in conjunction with 1) another developmental toxicity study in rats (CTL/P/576, MRID 00164903), and 2) information provided by Syngenta in their submission , DP 316263 (MRID 46527208), the following LOAELs/NOAELs were established for fomesafen.]** **Maternal NOAEL = 100 mg/kg/day** **Maternal LOAEL = 200 mg/kg/day based on staining of the ventral fur and significantly decreased body weight gain (>10%)** **Developmental NOAEL = 100 mg/kg bw/day** **Developmental LOAEL = 200 mg/kg bw/day based on postimplantation loss observed in study CTL/P/576 (MRID 00164903)**
870.3800 Reproduction and fertility effects - rat (2-generation)	**00144862 (1984) Acceptable/Guideline 0, 50, 250 or 1000 ppm (0, 2.5, 12.5 and 50 mg/kg/day)**	**Parental NOAEL = 250 ppm (12.5 mg/kg/day)** **Parental LOAEL = 1000 ppm (50 mg/kg/day) based on liver histopathology in males and females of both generations** **Offspring NOAEL = 250 ppm (12.5 mg/kg/day)** **Offspring LOAEL = 1000 ppm (50 mg/kg/day) based on increased incidence of liver hyalinization in males** **Reproductive NOAEL = 1000 ppm (50 mg/kg/day)** **Reproductive LOAEL was not established**
870.4200 Carcinogenicity mice - diet	**00131491 (1983) Acceptable/Guideline 0, 1, 10, 100 or 1000 ppm (0, 0.15, 1.5, 15 and 150 mg/kg/day)**	**NOAEL = 10 ppm (1.5 mg/kg/day)** **LOAEL = 100 ppm (15 mg/kg/day) based on the presence of liver tumors and liver weight increases in male and female mice**
870.4300 Chronic toxicity/ carcinogenicity rats - feeding	**00142125 (1984) Acceptable/Guideline 0, 5, 100 or 1000 ppm (0, 0.25, 5 and 50 mg/kg/day)**	**NOAEL = 5 ppm (0.25 mg/kg/day)** **LOAEL = 100 ppm (5 mg/kg/day) based on hyalinization of the liver in males**

4.2 FQPA Hazard Considerations

4.2.1 Adequacy of the Toxicity Data Base

The toxicology database for fomesafen is adequate for FQPA assessment. The following acceptable studies are available:

- Developmental toxicity study in rats
- 2 - Generation reproduction toxicity studies in rats

[There is an unacceptable/guideline developmental toxicity study in rabbits available that provides some information that fomesafen does not pose a hazard to the developing embryo.]

4.2.2 Evidence of Neurotoxicity

There is no concern for neurotoxicity resulting from exposure to fomesafen.

4.2.3 Developmental Toxicity Studies

a) Developmental Toxicity Studies in Rats

(MRID 00164903)

EXECUTIVE SUMMARY - In a developmental toxicity study (MRID 00164903), Fomesafen (97.5% a.i.) was administered to 17-24 pregnant rats/dose in corn oil by gavage at dose levels of 0, 50, 100 or 200 mg/kg bw/day from days 6 through 15 of gestation.

Maternal toxicity was evident at dose of 200 mg/kg bw/day (the highest dose tested) and was associated with staining of the ventral fur in 15 of 20 animals and significantly decreased body weight gain (>10%) during the dosing period (Days 7-16; Days16-21). Food consumption in the high-dose group was also significantly decreased as compared to the control group during the dosing period (Days 7-16; Days 16-21).

However, this study should be considered with: 1) Report Nos. CTL/P/656 and CTL/P/656S, MRID #001013016, and 2) information provided by Syngenta in their submission (DP 316263, MRID 46527208) in establishing the NOAEL and LOAEL (see Discussion/Added Information Section). With the additional information, the following conclusions can be made. **The maternal LOAEL is 200 mg/kg bw/day, based on staining of the ventral fur and significantly decreased body weight gain (>10%). The maternal toxicity NOAEL is 100 mg/kg bw/day. The developmental LOAEL is 200 mg/kg bw/day based on postimplantation loss. The developmental NOAEL is 100 mg/kg bw/day.**

This developmental toxicity study is classified **Acceptable/Guideline** and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rat in combination with another developmental toxicity in rat (MRID 001013016).

(MRID 00103016)

EXECUTIVE SUMMARY - In a developmental toxicity study (MRID 00103016), Fomesafen (97.5% a.i.) was administered to 19-21 pregnant rats/dose in corn oil by gavage at dose levels of 0, 1.0, 7.5 or 50 mg/kg bw/day from days 6 through 15 of gestation.

There was no maternal and/or fetal toxicity evident at any dose level tested. However, this study should be considered with: 1) Report No. CTL/P/576, MRID #00164903, and 2) information provided by Syngenta in their submission (DP 316263, MRID 46527208) in establishing the

NOAEL and LOAEL (see Discussion/Added Information Section). With the additional information, the following conclusions can be made. **The maternal LOAEL is 200 mg/kg bw/day, based on staining of the ventral fur and significantly decreased body weight gain (>10%). The maternal toxicity NOAEL is 100 mg/kg bw/day. The developmental LOAEL is 200 mg/kg bw/day based on postimplantation loss observed in study CTL/P/576 (MRID 00164903). The developmental NOAEL is 100 mg/kg bw/day.**

This developmental toxicity study is classified **Acceptable/Guideline** and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rat in combination with another developmental toxicity in rat (CTL/P/576, MRID 00164903).

b) Developmental Toxicity Study in Rabbits

(MRID 00109214)

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 00109214), fomesafen (97.5% a.i.) was administered to at least 13 pregnant Dutch rabbits/group orally (in gelatin capsules) at dose levels of 0, 2.5, 10, or 40 mg/kg/day from days 6 through 18 of gestation. Due to the low number of pregnant does in the low and high dose groups after the initial mating, 6 mated rabbits were added to the control, low, and mid dose groups and 7 to the high dose group. The remaining does were sacrificed on GD 29; their fetuses were removed by cesarean section and examined. A total of 17 animals died on study. Total mortality (including sacrifice *in extremis*) was 3/24, 3/24, 4/24, and 7/25 at 0, 2.5, 10, and 40 mg/kg/day, respectively. The incidence of mucous around the nose and/or forepaws increased in a dose-dependent manner: 3/24, 3/24, 4/24 and 8/25 at 0, 2.5, 10 and 40 mg/kg/day, respectively. Pasteurella multocida was isolated from two animals found dead or removed from the study prior to GD 29. However, no other animal was tested for infection with Pasteurella multocida. In the high dose group only, 6/25 does appeared thin, although body weight gain was not affected overall. Mean food consumption was 34% higher ($p<0.05$) than controls in the 40 mg/kg/day group during days 20-29. An increased incidence (6/25) of erosion of the stomach (hemorrhagic foci) was observed macroscopically in high dose females versus 1/24 in controls, 2/24 at 2.5 mg/kg/day, and 0/24 at 10 mg/kg/day. Erosion of the stomach was also observed in a separate, preliminary study at 75 and 150 mg/kg/day with an incidence of 7/12 animals at each dose.

The maternal LOAEL was unable to be determined due to the occurrence of an apparent bacterial infection in the animal colony.

There was no significant difference between the control and treated groups in pregnancy rate or abortions. While the mean number of implantations/dam was similar across dose, the number of corpora lutea/dam was significantly ($p<0.05$) increased in the high dose group (10.6) relative to controls (7.7). This resulted in an increase in pre-implantation loss at the high dose only. This observation was not considered toxicologically significant, because it suggested that dosing took place before the completion of implantation, resulting in maternal-stress-induced embryo lethality. Early and late fetal deaths increased in the mid-dose group only (7/24, 3/24, respectively) relative to controls (4/24, 1/24, respectively). There was an increased frequency of partially ossified hyoid (7.1%) and right vestigial rib (#13, 5.4%) at 40 mg/kg/day relative to

controls (2.9 and 0%, respectively). However, these variants are not regarded as toxicologically significant.

The developmental LOAEL was unable to be determined due to the occurrence of an apparent bacterial infection in the animal colony.

Because of an apparent bacterial infection in the animal colony; individual animal data were not reported; all fetuses were not examined for both soft tissue and skeletal alterations; and historical control data were not provided, the developmental toxicity study in the rabbit is classified **Unacceptable/guideline**. This study does not satisfy the guideline requirement for a developmental toxicity study [OPPTS 870.3700; §83-3(b)] in the rabbit.

4.2.4 Reproductive Toxicity Study

Rat 2-Generation Reproduction Study (MRID 00144862)

EXECUTIVE SUMMARY - In a two-generation reproduction toxicity study (MRID 00144862) Fomesafen (P28; 97.5% a.i.) was administered in diet to 30 Wistar rats (Alderley Park-derived)/sex/dose at dose levels of 0, 50, 250, or 1000 ppm (equivalent to 0, 2.5, 12.5, or 50 mg/kg/day) , for 2 generations. The F_1A pups were weaned on postnatal day (PND)22 and F_1B, F_2B and F_2A pups were weaned PND 29. Thirty F_1B females and 15 males were selected to become F_1 parents and produced F_2B litters. Brother-sister matings were avoided in each parental generation.

In the parental animals, no treatment-related effects were observed on body weights, or food consumption.

At 1000 ppm, an increased incidence of liver alterations were seen male and female F_0 and F_1 parents. These include congestion (M & F), multifocal necrosis (M), Kupffer cell pigmentation (M), hyalinization (diffuse and centrilobular; M & F) and biliary hyperplasia (M & F). An increased incidence of liver hyalinization was observed in the livers of F_1b males, however, these effects are considered to be of systemic effect rather than offspring toxicity. No liver alteration were observed at 250 ppm.

The parental LOAEL = 1000 ppm (50 mg/kg bw/day), based on liver histopathology in males and females of both generations. The maternal toxicity NOAEL = 250 ppm (12.5 mg/kg bw/day).

An increased incidence of liver hyalinization was observed in the livers of F_1b male pups. [Although, representative samples of liver from pups in the mid- and low-dose groups were not microscopically examined, hyalinization would not be expected to be observed since it was not observed in the livers of the parental animals in the low- and mid-dose groups.]

The offspring LOAEL = 1000 ppm (50 mg/kg/day), based on increased incidence of liver hyalinization in males. The offspring NOAEL = 250 ppm (12.5 mg/kg bw/day).

No treatment-related reproductive parameters were affected due to treatment with fomesafen. Reductions of litter size (15 - 20%) was observed in $F_1$and F_2 A litter at 250 ppm. A significant reduction (20%) in litter size was observed at 1000 ppm F_2B litters; however, there was no reduction in litter sizes in other 3 1000 ppm groups. A 13% reduction in litter size was also observed at 50 ppm in F_1 B litters. These litter reductions were sporadic, not dose-related, and therefore, considered to be of no toxicological significance. At 1000 ppm, an increased incidence of hyalinization of the liver was observed in F1B pups in the 1000 ppm group.

The reproductive NOAEL = 1000 ppm (50 mg/kg/day). The LOAEL was not established.

The study is classified **Acceptable/Guideline** and satisfies the guideline requirement for a reproduction toxicity (OPPTS 870.3800; OECD 416) for a two-generation reproduction study in the rat.

4.2.5 Additional Information from Literature Sources

There is no additional information on the toxicity of fomesafen that is currently available in the literature as demonstrated by a TOXNET search of 10/25/2005.

4.2.6 Pre-and/or Postnatal Toxicity

4.2.6.1 Determination of Susceptibility

The developmental toxicity study in rabbits is classified as unacceptable/guideline study due to bacterial infections and other minor deficiencies. However, in this study the maternal reproductive parameters of treated animals were comparable to controls. The results of the study did not indicate any evidence of increased susceptibility of rabbit fetuses due to the treatment with fomesafen. There is no evidence of qualitative and/or qualitative evidence of increased susceptibility of rat fetuses to *in utero* exposure to fomesafen. There is no evidence of increased qualitative and/or quantitative evidence of increased susceptibility to fomesafen following pre-natal exposure in a 2-generation reproduction study in rats.

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

The rabbit developmental toxicity study was compromised; however, the study provides information that fomesafen does not pose a hazard to the developing embryo. Therefore, it is concluded that there is no evidence of increased susceptibility to fomesafen following pre- and/or post-natal exposure. There are no concerns for residual uncertainties for pre- and/or post-natal susceptibility since there is no evidence of increased susceptibility.

4.3 Recommendation for a Developmental Neurotoxicity Study

There is no concern for neurotoxicity resulting from exposure to fomesafen.

4.3.1 Evidence That Supports Requiring a Developmental Neurotoxicity Study

None.

4.3.2 Evidence That Supports Not Requiring a Developmental Neurotoxicity Study

No indication of abnormalities in the development of the fetal nervous system was observed in the prenatal developmental toxicity studies in either rats or rabbits at dose levels up to 200 and 40 mg/kg/day, respectively.

No evidence of neuropathology was observed in the database.

A developmental neurotoxicity study in rats is not required.

4.4 Hazard Identification and Toxicity Endpoint Selection

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

Study Selected:

No toxic affects attributable to a single dose of fomesafen were found in the database; therefore, an endpoint and doses were not selected.

4.4.2 Acute Reference Dose (aRfD) - General Population

Study Selected:

No toxic affects attributable to a single dose of fomesafen were found in the database; therefore, an endpoint and doses were not selected.

4.4.3 Chronic Reference Dose (cRfD)

Study Selected: Combined Chronic Toxicity/Carcinogenicity - Rat §OPPTS 870.4300

MRID No.: 00142125

Executive Summary: In this combined chronic toxicity/carcinogenicity study (MRID 00142125), Fomesafen (97.5% a.i.; CTL Reference No. Y00053/001; Batch No. P28) was administered in the diet for 2 years to 52 Wistar albino rats/sex/dose at doses of 0, 5, 100 or 1000 ppm (equivalent to 0, 0.25, 5 and 50 mg/kg/day). In addition, groups of 12 rats/sex received the same dietary concentrations for up to 52 weeks (interim sacrifice).The actual concentrations of fomesafen in the test diets were in the acceptable range of 10% of the nominal concentrations.

There was an increased incidence of coat staining in males treated with 100 and 1000 ppm fomesafen and in all females treated with fomesafen. Body weights were significantly decreased in males in the 1000 ppm group from weeks 3 through 76. Decreased food utilization

efficiencies were observed in males treated with 100 and 1000 ppm fomesafen during the first 14 weeks of the study. Significant increases in the activities of plasma alkaline phosphatase, alanine
transaminase and aspartate transaminase, and in plasma albumin were observed in male rats treated with 1000 ppm fomesafen. Significant reductions in plasma cholesterol and triglycerides were observed in males and females treated with 1000 ppm fomesafen. Male and female rats treated with 1000 ppm fomesafen had depressed protein excretion in urine. Mean liver weights were significantly increased in males and females administered 1000 ppm fomesafen in the diet. Hyalinization of the liver was observed in rats administered 100 and 1000 ppm fomesafen in the diet. Biliary hyperplasia, bile duct dilatation and portal fibrosis were decreased in groups treated with 1000 ppm fomesafen. Pigmentation of portal macrophages, Kupffer cells, and hepatocytes was substantially increased in males and slightly increased in females treated with 1000 ppm fomesafen. **The LOAEL is 100 ppm (5 mg/kg/day), based on hyalinization of the liver in males. The NOAEL is 5 ppm (0.25 mg/kg/day).**

Dose and Endpoint for Establishing a cRfD: NOAEL = 0.25 mg/kg/day, based on hyalinization of the liver in males seen at the LOAEL of 5 mg/kg/day.

UF: 100 (10x for interspecies extrapolation; 10x for intraspecies variations).

Comments About Study/Endpoint and Uncertainty Factor: This study provides the lowest NOAEL in the database for chronic effects such as liver toxicity (hyalinization).

$$\textbf{Chronic RfD} = \frac{0.25 \text{ mg/kg (NOAEL)}}{100 \text{ (UF)}} = 0.0025 \text{ mg/kg/day}$$

4.4.4 Incidental Oral Exposure (Short and Intermediate Term)

Study Selected: 90 - Day Feeding - Rat § OPPTS 870.3100

MRID No.: 00103013

Executive Summary: In this subchronic toxicity study (MRID 00103013), Fomesafen (97.5% a.i.; PPO21) was administered in the diet for 90 days to 20 Alderley Park rats/sex/dose at doses of 0, 1, 5, 100 or 1000 ppm (equivalent to 0, 0.1, 0.5, 10 and 100 mg/kg/day). The animals were observed daily for clinical signs of toxicity. Body weights and food consumption were determined initially and at 2-week intervals, thereafter. Hematology, clinical chemistry and urinalysis were conducted. At termination, animals were necropsied, organs weighed and representative tissues examined microscopically. Election microscopy was conducted on selected tissues.

No mortality occurred. Animals in the 1000 ppm group gained less weight than the controls. Plasma alkaline phosphatase, alanine transaminase and aspartate transaminase were increased 169, 149 and 131%, respectively, in males in the 1000 ppm group. Liver weights were increased in male and females at 1000 ppm. Hyalinization of hepatocytes, increased eosinophilia and

reduced basophilic granulation was observed at 100 and 1000 ppm. Electron microscopy revealed an increase in peroxisomes in centrilobular hepatocytes at 100 and 1000 ppm. **The LOAEL is 100 ppm (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. The NOAEL is 5 ppm (0.5 mg/kg/day).**

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirements (OPPTS 870.3100; OECD 408) for a combined chronic toxicity/carcinogenicity study in rats.

Dose and Endpoint: The NOAEL is 0.5 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 seen at the LOAEL of 10 mg/kg/day.

Comments About Study/Endpoint: This endpoint would be appropriate for the route, duration of exposure (1-30 days; 1 - 6 months) and population of concern (infants and children), if residential uses were added to the use pattern.

4.4.5 Dermal Absorption

Dermal Absorption Factor: 20%

The dermal-absorption is estimated to be 20% based on the results of similar structurally related chemicals: acifluorfen (20% absorption rate) and oxifluorofen (18% absorption rate).

4.4.6 Dermal Exposure (Short and Intermediate Term)

Study Selected: Prenatal Developmental Toxicity-rat § OPPTS 870.3700

MRID No.: 00164903

Executive Summary: In a developmental toxicity study (MRID 00164903), Fomesafen (97.5% a.i.) was administered to 17-24 pregnant rats/dose in corn oil by gavage at dose levels of 0, 50, 100 or 200 mg/kg bw/day from days 6 through 15 of gestation.

Maternal toxicity was evident at dose of 200 mg/kg bw/day (the highest dose tested) and was associated with staining of the ventral fur in 15 of 20 animals and significantly decreased body weight gain (>10%) during the dosing period (Days 7-16; Days16-21). Food consumption in the high-dose group was also significantly decreased as compared to the control group during the dosing period (Days 7-16; Days 16-21).

However, this study should be considered with: 1) Report Nos. CTL/P/656 and CTL/P/656S, MRID #001013016, and 2) information provided by Syngenta in their submission (DP 316263,

MRID 46527208) in establishing the NOAEL and LOAEL (see Discussion/Added Information Section). With the additional information, the following conclusions can be made. **The maternal LOAEL is 200 mg/kg bw/day, based on staining of the ventral fur and significantly decreased body weight gain (>10%). The maternal toxicity NOAEL is 100 mg/kg bw/day. The developmental LOAEL is 200 mg/kg bw/day based on postimplantation loss. The developmental NOAEL is 100 mg/kg bw/day.**

Dose and Endpoint: The NOAEL is 100 mg/kg/day, based on postimplantation loss and significantly decreased maternal body weight gain seen at the LOAEL of 200 mg/kg/day.

UF: 100 (10x for interspecies extrapolation; 10x for intraspecies variations).

Comments About Study/Endpoint: No toxicity was seen in a 21-day dermal toxicity study in rats; however, the dermal toxicity study is not appropriate for dermal risk assessment because the dermal NOAEL (1000 mg/kg/day) would not be protective of the post implantation loss seen in the developmental toxicity study in rats at 200 mg/kg/day with a NOAEL of 100 mg/kg/day. Therefore, an oral endpoint was used. The dermal absorption factor of 20% would apply. [The dermal equivalent dose would be 500 mg/kg/day, which would be protective of the post implantation loss.]

4.4.7 Dermal Exposure (Long Term)

Study Selected: Combined Chronic Toxicity/Carcinogenicity - Rat § OPPTS 870.4300

MRID No.: 00142125

Executive Summary: See Section 4.4.3

Dose and Endpoint: The NOAEL is 0.25 mg/kg/day, based on hyalinization of the liver in males seen at the LOAEL of 5 mg/kg/day.

UF: 100 (10x for interspecies extrapolation; 10x for intraspecies variations).

Comments About Study/Endpoint: No toxicity was seen in a 21-day dermal toxicity study in rats. This study provides the lowest NOAEL in the database for chronic effects such as liver toxicity (hyalinization). In addition, the dermal toxicity study is not appropriate for dermal risk assessment because the dermal NOAEL (1000 mg/kg/day) would be not protective of the post implantation loss seen in the developmental toxicity study in rats at 200 mg/kg/day with a NOAEL of 100 mg/kg/day.

4.4.8 Inhalation Exposure (Short and Intermediate Term)

Study Selected: 90 - Day Feeding - Rat

§ OPPTS 870.3100

MRID No.: 00103013

Executive Summary: See Section 4.4.4.

Dose and Endpoint: The NOAEL is 0.5 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 seen at the LOAEL of 10 mg/kg/day.

UF: 100 (10x for interspecies extrapolation; 10x for intraspecies variations).

Comments About Study/Endpoint: No inhalation study is available in the database. The 90-day rat study was selected since the major toxic characteristics of fomesafen, liver toxicity, i.e., enzyme increases, eosinophilia and/or hyalinization begin to develop within this time frame.

4.4.9 Inhalation Exposure (Long Term)

Study Selected: Combined Chronic Toxicity/Carcinogenicity - Rat § OPPTS 870.4300

MRID No.: 00142125

Executive Summary: See Section 4.4.3

Dose and Endpoint: NOAEL = 0.25 mg/kg/day, based on hyalinization of the liver in males seen at the LOAEL of 5 mg/kg/day.

UF: 100 (10x for interspecies extrapolation; 10x for intraspecies variations).

Comments About Study/Endpoint: No inhalation study is available in the database. This study provides the lowest NOAEL in the database for chronic effects such as liver toxicity (hyalinization).

4.4.10 Margins of Exposure

The target Margins of Exposure (MOEs) for occupational exposure risk assessments are as follows:

Route	Short-Term	Intermediate-Term	Long-Term
	Occupational (Worker) Exposure		
Dermal	100	100	100

Inhalation	100	100	100
	Residential (Non-Dietary) Exposure		
Oral	-	-	-
Dermal	100	100	100
Inhalation	100	100	100

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

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

4.4.11 Recommendation for Aggregate Exposure Risk Assessments

No residential uses are proposed for fomesafen at this time. Therefore, aggregate risk consists of exposure from food and drinking water sources only. Acute and chronic aggregate risks were assessed. Occupational dermal and inhalation risks can not be aggregated because the endpoints are different.

4.4.12 Classification of Carcinogenic Potential

In accordance with the EPA Final Guidelines for Carcinogen Risk Assessment (March 29, 2005), the CARC classified Fomesafen as "Not Likely to be Carcinogenic to Humans". This decision was based on the weight-of-evidence which supports activation of peroxisome proliferator-activated receptor alpha (PPARα) as the mode of action for fomesafen-induced hepatocarcinogenesis in mice. The data did not support either mutagenesis or cytotoxicity followed by regenerative proliferation as alternative modes of action. While the proposed mode of action for liver tumors in mice is theoretically plausible in humans, it is quantitatively implausible and unlikely to take place in humans based on quantitative species differences in PPARα activation and toxicokinetics. The quantification of risk is not required.

Table 4.4 Summary of Toxicological Doses and Endpoints for Fomesafen for Use in Human Risk Assessments

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (females 13-49)	–	–	No toxic effects attributable to a single dose of fomesafen were found in the database.

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (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 = 100 Chronic RfD = 0.0025 mg/kg/day	FQPA SF = 1X (cPAD) = 0.00025 mg/kg/day	Chronic toxicity - rat LOAEL = 5 mg/kg/day based on hyalinization of the liver in males
Incidental Oral Short-Term (1 - 30 days)	NOAEL = 0.5 mg/kg/day	LOC for MOE = 100	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
Incidental Oral Intermediate-Term (1 - 6 months)	NOAEL = 0.5 mg/kg/day	LOC for MOE = 100	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
Dermal Short-Term (1 - 30 days)	NOAEL = 100 mg/kg/day (Dermal absorption rate = 20%)*	LOC for MOE = 100 (Occupational) LOC for MOE = 100 (Residential)	Prenatal developmental – rat LOAEL = 200 mg/kg/day based on postimplantation loss
Dermal Intermediate-Term (1 - 6 months)	NOAEL = 100 mg/kg/day (Dermal absorption rate = 20%)*	LOC for MOE = 100 (Occupational) LOC for MOE = 100 (Residential)	Prenatal developmental – rat LOAEL = 200 mg/kg/day based on postimplantation loss
Dermal Long-Term (> 6 months)	NOAEL = 0.25 mg/kg/day (Dermal absorption rate = 20%)*	LOC for MOE = 100 (Occupational) LOC for MOE = 100 (Residential)	Chronic toxicity - rat LOAEL = 5 mg/kg/day based on hyalinization of the liver in males
Inhalation Short-Term (1 - 30 days)	NOAEL = 0.5 mg/kg/day (Inhalation adsorption rate = 100% oral equivalent)	LOC for MOE = 100 (Occupational) LOC for MOE = 100 (Residential)	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

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Inhalation Intermediate-Term (1 - 6 months)	NOAEL = 0.5 mg/kg/day (Inhalation adsorption rate = 100% oral equivalent)	LOC for MOE = 100 (Occupational) LOC for MOE = 100 (Residential)	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
Inhalation Long-Term (> 6 months)	NOAEL = 0.25 mg/kg/day (Inhalation adsorption rate = 100% oral equivalent)	LOC for MOE = 100 (Occupational) LOC for MOE = 100 (Residential)	Chronic toxicity - rat LOAEL = 5 mg/kg/day based on hyalinization of the liver in males
Cancer (oral, dermal, inhalation)	**Classification:** The CARC classified Fomesafen as "Not Likely to be Carcinogenic to Humans."		

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse-effect level, LOAEL = lowest observed adverse-effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable
* Refer to Section 4.5

4.5 Special FQPA Safety Factor

Based on the hazard data, the fomesafen risk assessment team recommended the special FQPA SF be reduced to 1x because there is no concern and/or residual uncertainty with regard to pre- and/or postnatal increased susceptibility. The requirement for an acceptable "guideline" developmental toxicity study in a second species has not been satisfied. The previously submitted study in rabbits (MRID 00109214) has been reevaluated and has been found to be deficient. Individual animal data were not reported and all fetuses were not examined for both soft tissue and skeletal alterations; and historical control data were not provided. Additionally, animals had an intercurrent infection that confounded interpretation of the results of the study. Therefore, the developmental toxicity study in the rabbit was classified Unacceptable/Guideline. However, a new developmental toxicity study in rabbits is not required at this time because the reproductive parameters of treated dams were comparable to controls. This study does provide adequate information that fomesafen does not pose a hazard to the developing embryo.

4.6 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 fomesafen, 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, fomesafen may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

5.0 Public Health Data

5.1 Incident Reports

Incident reports will be addressed in a separate memorandum.

6.0 Exposure Characterization/Assessment

6.1 Dietary Exposure/Risk Pathway

6.1.1 Residue Profile

Residue chemistry consideration are contained in the memorandum entitled *Fomesafen Sodium. Residue Chemistry Summary for the HED Human Health Risk Assessment, a Proposal To Amend Use on Soybeans, and Proposals to Add Uses on Cotton, Dry Bean, and Snap Bean. PP#1E6228, PP#9F5068, and PP#6E4653* (D. Davis, D325801).

The nature of the residue in soybean seed is adequately understood based on acceptable metabolism studies with soybeans. Additional information is required to support the submitted cotton metabolism study. Fomesafen was found to be extensively metabolized in soybean seed; the metabolism study demonstrated the incorporation of radioactivity into triglycerides (fatty acids and glycerol), proteins (amino acids), starch, cellulose, lignin, and soluble carbohydrate fractions. Based on these data, the residue of concern in soybean seed, dry bean, and snap bean is fomesafen *per se*.

The nature of the residue in cotton gin byproducts has been addressed in a cotton metabolism study. This study is currently classified as unacceptable, but upgradeable. For the purpose of this action, information on the likely metabolic profile of fomesafen in cotton byproducts can be elucidated. Provided the requested additional information continues to support the findings in the study, it appears that in cotton, fomesafen is metabolized in cotton via hydrolysis of the

biphenyl ether linkage, which would yield 2-chloro-4-(trifluoromethyl)phenol. This compound is then conjugated with uridine diphosphate glucose to form 1-[2-chloro-4-(trifluoromethyl)phenyl]-β-D-glucopyranoside. Metabolite D would then be formed via sulfate transfer from 3'-phosphoadenylsulfate to the C-6 position of glucose, also yielding adenosine-3',5'-biphosphate.

The submitted soybean metabolism study only investigated metabolism in soybean seed, and not in forage and hay, and the cotton metabolism study only investigated metabolism in gin byproducts because of low radioactivity levels in seed. Therefore, HED concludes that these studies may only be used to support the proposed/registered uses on cotton, dry and snap beans, and soybean. **If Syngenta wishes to propose additional food/feed uses of fomesafen sodium in the future, additional plant metabolism studies may be required.**

The nature of the residue in livestock is adequately understood based on acceptable metabolism studies in goats and hens. The significant residues found in highly exaggerated rate studies in livestock commodities consists of fomesafen and its metabolites 5-(2-chloro-α,α,α-trifluoro-p-tolyloxy) anthranilic acid (compound V) and 5-(2-chloro-α,α,α-trifluoro-p-tolyloxy)-N-methylsulfonylanthranilamide (compound XV). In consideration of the residue levels in goat and hen matrices following dosing at ~515x and ~1300x the maximum theoretical dietary burden to cattle and poultry, respectively, HED concludes that the proposed/registered uses of fomesafen on cotton, dry and snap beans, and soybeans result in a 40 CFR §180.6(a)(3) situation for livestock commodities; i.e., there is no reasonable expectation of finite residues in livestock commodities. Livestock feeding studies are not required to support the proposed and registered uses of fomesafen.

The available enforcement analytical method for crop matrices, a high performance liquid chromatography method with UV detection (HPLC/UV), GAM-RM-001/86, is adequate for data collection and has passed Agency validation. Syngenta has submitted a new enforcement method, a gas chromatography method with nitrogen/phosphorus detection (GC/NPD), TMR0836B, for determination of residues of fomesafen in/on soybean commodities. The proposed enforcement method differs from the existing enforcement method in the use of GC/NPD for analysis of extracts, resulting in a lower limit of quantitation (LOQ). The extraction procedures of the proposed enforcement method are similar to those of the existing method; however, in the proposed method, fomesafen is converted to its methylated analog to allow GC determination. The proposed enforcement method may be used for enforcement of the proposed tolerances for dry bean and snap bean. Syngenta has proposed a similar GC/NPD method, TMR0800B, for the determination of residues of fomesafen in cotton commodities. Raw data are required to support the method validation data that were submitted for the proposed enforcement methods. Because the extraction procedures of the methods are similar to those of the existing enforcement method, petition method validation of the proposed enforcement methods will not be required.

Methods for the determination of fomesafen residues in livestock commodities are not required.

Adequate crop field trial data have been submitted for dry bean, snap bean, and soybean

reflecting the proposed uses; additional data are required to support the crop field trial data submitted for cotton. All crop field trial studies are supported by adequate storage stability data. The soybean crop field trial data indicate that a tolerance for soybean aspirated grain fractions is needed. Adequate processing data have been submitted for cotton and soybean which indicate that quantifiable residues of fomesafen are not likely in the processed commodities of cotton and soybean. The residue data are summarized below in Table 6.1.1.

Table 6.1.1 Summary of Residues from Crop Field Trials with Fomesafen Sodium.

Crop Matrix	Applic. Method/ Timing	Applic. Rate (lb ai/A)	PHI (days)	Residues (ppm)						
				n	Min.	Max.	HAFT[1]	Median	Mean	Std. Dev.
Cotton (proposed use = 0.5 lb ai/A total application rate, 70-day PHI)										
Cotton, undelinted seed	Preplant incorporated	0.46-0.5	134-179	24	<0.025	<0.025	<0.025	0.025	0.025	0
		1	134-179	5	<0.025	<0.025	<0.025	0.025	0.025	0
	Broadcast soil	0.46-0.5	134-171	24	<0.025	0.031[2]	<0.028	0.025	0.025	0
	Directed post	0.5	71-113	24	<0.025	<0.025	<0.025	0.025	0.025	0
Cotton, gin byproducts	Preplant incorporated	0.46-0.5	134-179	12	<0.02	<0.02	<0.02	0.02	0.02	0
		1	179	2	<0.02	<0.02	<0.02	0.02	0.02	--
	Broadcast soil	0.46-0.5	134-171	12	<0.02	<0.02	<0.02	0.02	0.02	0
	Directed post	0.5	71-113	12	<0.02	0.02	<0.02	0.02	0.02	0
Dry bean (proposed use = 0.375 lb ai/A total application rate, 30-day PHI)										
Dry bean	Postemergence foliar	0.313-0.375	63-82	6	<0.026	<0.026	<0.026	0.026	0.026	0
		0.375	45-48	28	<0.02	<0.02	<0.02	0.02	0.02	0
Snap bean (proposed use = 0.375 lb ai/A total application rate, 30-day PHI)										
Snap bean	Postemergence foliar, prebloom	0.25-0.38	24-34	14	<0.025	<0.025	<0.025	0.025	0.025	0
		0.375	28-31	10	<0.02	<0.02	<0.02	0.02	0.02	0
Soybean (proposed use = 0.375 lb ai/A total application rate, 45-day PHI)										
Soybean seed	Preplant incorporated	0.5	108-159	40	<0.02	<0.02	<0.02	0.02	0.02	0
	Postemergence broadcast foliar	0.5	35-48	40	<0.02	<0.02	<0.02	0.02	0.02	0
Soybean aspirated grain fractions	Postemergence broadcast foliar	0.5	48	3	<0.020	0.041	0.029	0.025	0.029	0.011

[1] HAFT = Highest Average Field Trial.
[2] Sample was reanalyzed and yielded a residue of <0.025 ppm.

The nature of the residue in rotated crops has not been adequately addressed. The existing confined rotational crop data are not adequate, nor are they upgradeable. For the purposes of this registration, HED has advised the registrant that the label rotational crop restrictions need to be revised to permit immediate replanting of soybeans, cotton, dry beans and snap beans only with a restriction that other crops can only be planted 12 months after treatment or 18 months after treatment if based on phytotoxicity concerns.

6.1.2 Acute and Chronic Dietary Exposure and Risk

The dietary exposure assessment to support this human health risk assessment is detailed a memorandum entitled ***Fomesafen Sodium****: Chronic Dietary Exposure Assessment for the HED Human Health Risk Assessment* (T. Goodlow, 2/15/06, D325798).

Chronic dietary risk assessments were conducted 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.

No toxic affects attributable to a single dose of fomesafen could be found in the toxicity database; therefore, an acute dietary exposure assessment was not performed. The Cancer Assessment Review Committee (CARC) classified fomesafen as "Not likely to be carcinogenic to humans"; therefore, a cancer assessment was not performed.

Chronic Dietary Exposure Results and Characterization

Chronic dietary exposure assessments were performed for fomesafen sodium. 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 PAD. Detailed results of the chronic dietary exposure and risk estimates for exposure from food only are detailed below in Table 6.1.2.

Table 6.1.2 Results of Chronic Dietary Exposure and Risk Estimates for Fomesafen Sodium Using DEEM-FCID- Food Only

Population Subgroup [1]	PAD, mg/kg/day	Exposure, mg/kg/day	% PAD
U.S. Population	0.0025	0.000017	<1
All infants (< 1 yr)	0.0025	0.000038	1.5
Children 1-2 yrs	0.0025	**0.000041**	**1.6**
Children 3-5 yrs	0.0025	0.000035	1.4
Children 6-12 yrs	0.0025	0.000023	<1
Youth 13-19 yrs	0.0025	0.000015	<1
Adults 20-49 yrs	0.0025	0.000013	<1
Adults 50+ yrs	0.0025	0.000012	<1
Females 13-49 yrs	0.0025	0.000013	<1

[1] The values for the population with the highest risk for each type of risk assessment are bolded.

6.2 Water Exposure/Risk Pathway

EFED's assessment of potential drinking water impacts from the proposed uses of fomesafen is detailed in the memorandum entitled *Tier II Drinking Water Assessment for Fomesafen use on cotton, soybeans, dry beans and snap beans* (J. Hetrick, 9/27/05, D314014)

Environmental fate data indicate that fomesafen should be very mobile and highly persistent in terrestrial and aquatic environments. The major routes of dissipation from the application site are expected to be runoff and leaching. To support this action, EFED conducted a Tier II drinking water assessment.

The surface water assessment was conducted using environmental fate data in the PRZM-EXAMS model. There is a complete environmental fate data base except for the a sediment half-life value. The surface water modeling was conducted on standard EFED scenarios for cotton in TX, NC, MS and soybeans in MS. These scenarios were selected because they are expected to be representative of use sites prone to high runoff as well as representative of the highest regional use rates for fomesafen. Application rates were selected to reflect a maximum application rate of 0.375 lbs ae/A. Fomesafen aerial applications were simulated to account for spray drift of fomesafen to surface waters. The half life of fomesafen in sediment was assumed to be stable. No surface water monitor data were available for fomesafen. Surface Water estimated environmental concentrations (EECs) for fomesafen are shown in Table 6.2, below.

Table 6.2 Surface Water EDWCs for Fomesafen Sodium Using PRZM-EXAMS

Crop	Peak	90 Day Average	Annual Average	30 Year Average
	ppb (µg/L)			
Soybeans (MS)	15.489	12.177	6.574	3.364
Cotton (MS)	25.167	19.178	**10.535** [1]	5.609
Cotton (NC)	20.488	15.312	9.735	5.443
Cotton (TX)	25.372	18.612	8.615	3.873

[1] Represents value used in dietary assessment

EFED conducted a ground water assessment using the available environmental fate data and the SCI-GROW model. EFED notes that although the K_{oc} model is inappropriate for estimation of fomesafen soil-water partitioning, the lowest reported K_{oc} was used in the assessment. The SCI-GROW modeling indicated that peak and long-term average concentrations of fomesafen in shallow ground water were not expected to exceed 11.2 µg/L. No USGS groundwater monitoring data were located for fomesafen, however, the registrant submitted a prospective monitoring study for fomesafen use on soybeans in North Carolina which clearly showed that fomesafen has a potential to leach to ground water. Fomesafen was detected at concentrations of 1 µg/L, which is the detection limit for the compound. The detections were confirmed using an alternate analytical technique. EFED recommends using the ground water monitoring concentration of 1 µg/L as the benchmark concentration for fomesafen in ground water source drinking water because it represents actual use conditions of fomesafen on soybeans on a vulnerable soil.

6.3 Residential (Non-Occupational) Exposure/Risk Pathway

6.3.1 Home Uses

There are no residential uses for fomesafen sodium; therefore, an evaluation of exposures resulting from home uses was not required.

6.3.12 Recreational Uses

There are no residential uses for fomesafen sodium; therefore, an evaluation of exposures resulting from recreational uses was not required.

6.3.1 Spray Drift

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for fomesafen. 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. On a chemical by chemical basis, the Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new data base submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift with specific products with significant risks associated with drift.

7.0 Aggregate Risk Assessments and Risk Characterization

7.1 Acute Aggregate Risk

There were no observed effects which were the result of a single exposure to fomesafen, therefore an acute aggregate risk assessment is not required.

7.2 Short-, Intermediate-Term Aggregate Risk

There are currently no registered residential uses for fomesafen; therefore short- and intermediate- term aggregate risk assessments are not required.

7.3 Long-Term Aggregate Risk

There are currently no registered residential uses for fomesafen; therefore, the long-term aggregate risk should consider residues from food and water alone. To determine the chronic aggregate risk, an additional DEEM-FCID™ analysis was conducted which directly incorporated estimated drinking water concentrations (EDWCs) from the Environmental Fate and Effects Division. The dietary exposure analyses in this assessment resulted in 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 chronic population adjusted dose (cPAD); and the exposure for food plus ground water was 0.000107 mg/kg/day, which utilized 4.3% of the cPAD. For this same group, "all infants" the food only exposure was 0.000038 mg/kg/day, which utilized 1.5% of the cPAD. A summary of the chronic dietary exposure assessment is provided in Table 7.1, below.

Table 7.1 Summary of Chronic Dietary Exposure and Risk for Fomesafen Sodium Incorporating Surface and Ground Water As Drinking Water Sources

Population Subgroup [1]	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
All Infants (< 1 year old)	10.535	**0.000766**	**31**	1.0	**0.000107**	**4.3**
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

[1] The values for the population with the highest exposure for each type of risk assessment are bolded.

7.4 Cancer Risk

The CARC has classified fomesafen as "Not Likely to be Carcinogenic to Humans"; therefore, a cancer risk assessment is not required.

8.0 Cumulative Risk Characterization/Assessment

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to fomesafen and any other substances and fomesafen 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 fomesafen has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

9.0 Occupational Exposure/Risk Pathway

The details of the occupational exposure and risk assessment are contained in the memorandum entitled ***Fomesafen****: Occupational and Residential Exposure and Risk Assessment for the Registration for New Uses on Drybeans, Snapbeans, and Cotton* (M. Lloyd, 2/15/06, D294458).

There is potential for occupational exposure to fomesafen during mixing, loading, application, and postapplication activities. For short-/intermediate-term inhalation exposure, HED selected an endpoint from a 90 day rat oral study (NOAEL = 0.5 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 aspartame transaminase in males at 10 mg/kg/day. For short-/intermediate-term dermal exposure, HED selected endpoints from the prenatal developmental toxicity study in the rat. An endpoint from an oral study was selected since the endpoints and doses selected from the 21-day dermal toxicity study in rats would not be protective of the post implantation loss seen in the developmental toxicity study in rats. The NOAEL selected was 100 mg/kg/day, based on post implantation loss and significantly decreased maternal body weight gain seen at the LOAEL of 200 mg/kg/day. For long-term dermal and inhalation exposure, the endpoint was selected from a chronic rat toxicity study (NOAEL = 2.5 mg/kg/day), based on hyalinization of the liver in males. Because the dermal endpoints were selected from oral studies, daily dermal doses were adjusted to account for 20% dermal absorption. The dermal and inhalation MOEs were calculated separately because the dermal and inhalation endpoints were based upon different effects. The level of concern (LOC) for short-/intermediate-term and long-term exposure is for MOEs of less than 100.

The Cancer Assessment Review Committee (CARC) classified fomesafen as "not likely to be carcinogenic to humans", and quantification of cancer risk was not required.

No chemical-specific handler exposure data were submitted in support of this registration. For the use assessment, data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 as presented in PHED Surrogate Exposure Guide (8/98) was used.

While endpoints were selected for chronic exposures, these endpoints were not used in this assessment. Fomesafen is typically applied early in the growing season and chronic occupational exposures to fomesafen would not be expected to occur. The MOEs for occupational exposures were calculated for short/intermediate term dermal and inhalation exposures. These MOEs were calculated separately because the dermal and inhalation endpoints were based upon different effects. Standard assumptions, PHED unit exposure data and maximum label rates were used.

The MOEs for handlers are summarized in Tables 9.1.

Table 9.1 Fomesafen: Short-/Intermediate-term Dermal and Inhalation Risks for Agricultural Handler Activities							
Exposure Scenario	**Daily Area Treated (Acres/ day)**	**Crop**	**Application Rate (lb ae/A)**	**Short-/Intermediate-term Risk Estimate**			
				Dermal MOE (Target MOE = 100)		**Inhalation MOE (Target MOE = 100)**	
				Baseline	**Single Layer PPE**	**Baseline**	**PF5**
Mixing/Loading (M/L)							
M/L Liquids for Aerial applications	1200	Cotton, dry/snap beans, soybeans	0.375 (Region I & II)	27	3400	65	320
		Dry beans, snap beans, soybeans	0.313 (Region III)	32	4100	78	390
			0.25 (Region IV)	40	5100	97	490
			0.1875 (Region V)	54	6800	130	650
M/L Liquids for Groundboom application	200	Cotton, dry/snap beans, soybeans	0.375 (Region I & II)	161	20000	390	1900
		Dry beans, snap beans, soybeans	0.313 (Region III)	190	24000	470	2300
			0.25 (Region IV)	240	30000	580	2900
			0.1875 (Region V)	320	41000	780	3900

Table 9.1 Fomesafen: Short-/Intermediate-term Dermal and Inhalation Risks for Agricultural Handler Activities

Exposure Scenario	Daily Area Treated (Acres/ day)	Crop	Application Rate (lb ae/A)	Short-/Intermediate-term Risk Estimate			
				Dermal MOE (Target MOE = 100)		Inhalation MOE (Target MOE = 100)	
				Baseline	Single Layer PPE	Baseline	PF5
Applicator							
Aerial Application (closed cockpit)	1200	Cotton, dry/snap beans, soybeans	0.375 (Region I & II)	16000	NA	1100	NA
		Dry beans, snap beans, soybeans	0.313 (Region III)	19000		1400	
			0.25 (Region IV)	23000		1700	
			0.1875 (Region V)	31000		2300	
Groundboom Application (open cab)	200	Cotton, dry/snap beans, soybeans	0.375 (Region I & II)	33000	33000	630	3200
		Dry beans, snap beans, soybeans	0.313 (Region III)	40000	40000	760	3800
			0.25 (Region IV)	50000	50000	950	4700
			0.1875 (Region V)	67000	67000	1300	6300
Flagger							
Flagging for Aerial Applications	1200	Cotton, dry/snap beans, soybeans	0.375 (Region I & II)	7000	7000	220	1100
		Dry beans, snap beans, soybeans	0.313 (Region III)	8500	8500	270	1300
			0.25 (Region IV)	11000	11000	330	1700
			0.1875 (Region V)	14000	14000	440	2200

The dermal MOEs for mixer/loader with baseline PPE for aerial application on cotton and beans were below 100 and single layer PPE is required to achieve acceptable MOEs. All of the dermal MOEs are acceptable with single layer PPE for handlers and baseline PPE for applicators and flaggers. The proposed label calls for single layer PPE for agricultural handlers. Most of the inhalation MOEs for the mixer/loader scenarios for aerial application are of concern with baseline PPE, and PF5 respirators are required to achieve acceptable MOEs. The remaining scenarios are not of concern with baseline PPE and respirators are not required.

Post-application exposure for re-entry workers is possible for fomesafen. Post-application activities including irrigation and scouting, among other activities, that can result in dermal exposures. The exposures were assessed using standard assumptions and the maximum label rate. No data was available so the initial percent of application rate as Dislodgeable Foliar Residue (DFR) was assumed to be 20% for all crops.

Table 9.3 Fomesafen Post-application Short/Intermediate Term Risks

Crop Group	Application Rate (lb ai/A)	MOE on Day 0			
		Low	Medium	High	Very High
Field/Row Crops, Low/Medium (soybeans, cotton)	0.375	>1000	700	N/A	N/A
Field/Row Crops, Low/Medium (dry/snap beans)	0.375	>1000	700	420 (snap beans only)	N/A

There are no post-application risks of concern for fomesafen. All of the post-application MOEs are greater than 100 on Day 0. Hand harvesting dry/snap beans is an activity with the lowest MOE of 420 on Day 0. The proposed label proposes an REI of 24 hours.

All worker exposure assessments were conducted using the maximum proposed rate of 0.375 lb ai/acre and several additional region specific rates. Typical rates are expected to be lower particularly if fomesafen is tank mixed with other products (e.g.-Basagram). The proposed product label requires waterproof gloves instead of chemical resistant gloves. It is not known if these gloves provide adequate protection. **It is recommended that mixers and loaders wear gloves made of chemically resistant and waterproof material when handling fomesafen.**

10.0 Data Needs and Label Requirements

10.1 Toxicology

The following toxicology data gaps exist:

869.1200 Acute Dermal Toxicity Study

870.1300 Acute Inhalation Toxicity Study

869.2600 Skin Sensitization Study

870.7600 Dermal Penetration Study

10.2 Residue Chemistry

Provided the following deficiencies are addressed as a condition of the registration, HED concludes that the residue chemistry database is sufficient to support requested Section 3 registration and establishment of tolerances for residues of fomesafen sodium in/on soybeans, cotton, dry beans and snap beans.

- The following revisions to the Reflex® Herbicide label are required before the directions for use can be approved*.
    - At this time, data are not available to support rotation to other crops beyond those commodities that are currently proposed as primary crops; therefore the registrant must revise the Reflex® Herbicide label to permit immediate replanting of soybeans, cotton, dry beans and snap beans only with a restriction that other crops can only be planted 12 months after treatment or 18 months after treatment if based on phytotoxicity concerns.
    - At this time, data are not available to support the PHI requested for dry beans; therefore the registrant must revise the label to specify a 45-day PHI for dry beans.
    - The proposed use directions for snap beans must be amended to remove Frontier as a recommended tank mix partner.

*Note: The current label contains the following restriction: "Do not graze treated areas or harvest forage or hay". HED does not typically consider this type of general grazing restriction to be practical. Since residue data have not been provided for either soybean or cowpea forage or hay, and since HED does consider it practical, and in this case necessary, to restrict grazing for those commodities, a grazing restriction is required for the Reflex® Herbicide label. However, as noted above, the requested rotational crop restrictions are not currently supported by data and must be removed; therefore when the required amendment is made to restrict rotation only to those crops for which fomesafen is registered, the registrant may leave the general restriction on the label since it would only be applicable to the commodities for which HED considers it practical to restrict grazing. However, at such time as adequate rotational crop data are available, or should additional crops be added to the label, the registrant will be required to provide a more specific grazing restriction limited to soybean forage/hay and cowpea forage/hay.

- The cotton metabolism data are inadequate to satisfy data requirements. The study may be upgraded with the submission of the following additional information:
    - The actual application rate for the higher treatment rate must be provided (Syngenta only provided the target application rate for plants treated at 1.5 lb ai/A). The lighting and temperature conditions used in the greenhouse should be provided.
    - Syngenta must provide the dates of sample analysis for all samples and all analyses. If final analyses of cotton gin byproduct samples were not completed within 6 months of sample collection, Syngenta must provide evidence that the metabolite profile in samples did not change during storage. We note that based on the study completion date, samples may have been stored >500 days prior to final analysis.

- There was a large difference between the total extractable radioactivity and the total of the identified and characterized radioactivity for each sample. For samples treated at the lower rate, Syngenta referred to this "fraction" as "total % unknown." The total unknown fraction ranged 11.0-49.5% TRR (0.009-0.112 ppm) in gin byproduct samples. No explanation was provided. Syngenta also did not provide any quantitative chromatographic raw data. Syngenta must provide an explanation for this apparent loss in radioactivity. In addition, quantitative chromatographic data should be provided for all chromatograms included in the submission.
- Syngenta should provide an interpretation of the LC/MS spectra that were included in the submission for Metabolites B-3 and C-1 and provide proposed structures for these metabolites, if possible.
- Syngenta should provide an explanation for not making any attempts to characterize the nonextractable radioactivity in gin byproducts treated with NP label [^{14}C]fomesafen at the higher rate. According to the requirements of OPPTS 860.1300, additional attempts to extract this radioactivity should have been made (nonextractable radioactivity was >10% TRR and >0.05 ppm).

- Syngenta must submit raw data to support the method validation data reported in MRIDs 44754703, 45093602, 45093603, 45268502 and 45268503.

- Syngenta should modify GC/NPD Method No. TMR0836B to include instructions for the extraction and analysis of dry bean, snap bean, and soybean aspirated grain fractions. The modified method should then be forwarded to FDA for inclusion in the Pesticide Analytical Manual (PAM) Volume II.

- Syngenta must submit multiresidue method testing data for fomesafen.

- Data are required depicting the stability of residues of fomesafen in/on the following commodities: cotton gin byproducts stored frozen for up to 11 months; soybean hulls and oil stored frozen for up to 10 months; corn cob stored frozen for up to 7 months; wheat forage and straw during frozen storage for up to 13 months; and field corn or sorghum forage and stover during frozen storage for up to 10 months.

- The following data are required to upgrade the available crop field trial data to support the proposed use on cotton.
  - A summary of weather conditions at the individual sites, indication as to whether irrigation was used, and average historical data for temperature and rainfall for the duration of the field intervals of the trials.
  - Soil characteristics data (percent organic matter, pH, and cation exchange capacity) for the individual sites.
  - Raw data including at least: (i) field notes and/or reports on application (including which spray adjuvant was used), plot maintenance, and sample harvest; (ii) calibration of application equipment (for confirmation of application rate); and (iii) a specific description (which may be in the field notes) as to how

and where (within the plot) the sample was taken and what was done to ensure that samples were representative of the test plot.

- If the registrant wishes to allow rotation to crops which do not have Section 3 registrations, Syngenta must conduct a new confined rotational crop study. The study should reflect separate application of CP- and NP-label fomesafen at the maximum seasonal application rate to rotatable crops. The study should include the plantback intervals (PBIs) that Syngenta wishes to include on product labels, up to 12 months. For complete guidance on the conduct of the study, OPPTS GLN 860.1850 should be conducted.

10.3 Occupational and Residential Exposure

The proposed product label should be revised to require chemical resistant gloves.

References:

Fomesafen: Second Report of the Cancer Assessment Review Committee, TXR No. 0053835, J. Kidwell, 11/3/2005

Fomesafen: Occupational and Residential Exposure and Risk Assessment for the Registration for New Uses on Drybeans, Snapbeans, and Cotton, D294458, M. Lloyd, 2/15/2006

Fomesafen Sodium. Residue Chemistry Summary for the HED Human Health Risk Assessment, a Proposal To Amend Use on Soybeans, and Proposals to Add Uses on Cotton, Dry Bean, and Snap Bean, D325801, D. Davis

Fomesafen Sodium: Chronic Dietary Exposure Assessment for the HED Human Health Risk Assessment, D325798, T. Goodlow, 2/15/2006

Tier II Drinking Water Assessment for Fomesafen use on cotton, soybeans, dry beans, and snap beans, D314014, J. Hetrick, 9/27/2005

Usage Report in Support of Reregistration for the Herbicide, Fomesafen Sodium (123802), J. O'Neill, 8/30.2005

Appendices

Appendix 1. Toxicological Data Requirements

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The requirements (40 CFR 158.340) for Food Use for fomesafen are presented below. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Test		Technical	
		Required	Satisfied
870.1100		yes	yes
	Acute Oral Toxicity	yes	no
870.1200		yes	no
	Acute Dermal Toxicity	yes	yes
870.1300		yes	yes
	Acute Inhalation Toxicity	yes	no
870.2400			
	Primary Eye Irritation		
870.2500			
	Primary Dermal Irritation		
870.2600			
	Dermal Sensitization		
870.3100		yes	yes
	Oral Subchronic (rodent)	yes	yes
870.3150		yes	yes
	Oral Subchronic (nonrodent)	no	-
870.3200		no	-
	21-Day Dermal		
870.3250			
	90-Day Dermal		
870.3465			
	90-Day Inhalation		
870.3700a		yes	yes
	Developmental Toxicity (rodent)	yes	no
870.3700b		yes	yes
	Developmental Toxicity (nonrodent)		
870.3800			
	Reproduction		
870.4100a		yes	yes
	Chronic Toxicity (rodent)	yes	yes
870.4100b		yes	yes
	Chronic Toxicity (nonrodent)	yes	yes
870.4200a		yes	yes
	Oncogenicity (rat)		
870.4200b			
	Oncogenicity (mouse)		
870.4300			
	Chronic/Oncogenicity		

Test	Technical	
	Required	Satisfied
870.5100	yes	yes
Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	yes	yes
Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5xxx		
Mutagenicity—Structural Chromosomal Aberrations		
870.5xxx		
Mutagenicity—Other Genotoxic Effects		
870.6100a	no	-
Acute Delayed Neurotox. (hen)	no	-
870.6100b	no	-
90-Day Neurotoxicity (hen)	no	-
870.6200a	no	-
Acute Neurotox. Screening Battery (rat)		
870.6200b		
90 Day Neuro. Screening Battery (rat)		
870.6300		
Develop. Neuro		
870.7485	yes	yes
General Metabolism	yes	no
870.7600		
Dermal Penetration		
Special Studies for Ocular Effects		
Acute Oral (rat)	no	-
	no	-
Subchronic Oral (rat)	no	-
Six-month Oral (dog)		

Appendix 2. Toxicology Studies

MRID No. **Citation**

00103013 Wade, J.; Banham, P.; Chart, I.; et al. (1981) PP021: 90 Day Feeding Study in Rats: Report No. CTL/P/554. (Unpublished study received May 28, 1982 under 10182-EX-30; prepared by Imperial Chemical Industries, Ltd., Eng., submitted by ICI Americas, Inc., Wilmington, DE; CDL:247589-E). Unpublished.

EXECUTIVE SUMMARY - In this subchronic toxicity study (MRID 00103013), Fomesafen (97.5% a.i.; PPO21) was administered in the diet for 90 days to 20 Alderley Park rats/sex/dose at doses of 0, 1, 5, 100 or 1000 ppm (equivalent to 0, 0.1, 0.5, 10 and 100 mg/kg/day). The animals were observed daily for clinical signs of toxicity. Body weights and food consumption were determined initially and at 2-week intervals, thereafter. Hematology, clinical chemistry and urinalysis were conducted. At termination, animals were necropsied, organs weighed and representative tissues examined microscopically. Election microscopy was conducted on selected tissues.

No mortality occurred. Animals in the 1000 ppm group gained less weight than the controls. Plasma alkaline phosphatase, alanine transaminase and aspartate transaminase were increased 169, 149 and 131%, respectively, in males in the 1000 ppm group. Liver weights were increased in male and females at 1000 ppm. Hyalinization of hepatocytes, increased eosinophilia and reduced basophilic granulation was observed at 100 and 1000 ppm. Electron microscopy revealed an increase in peroxisomes in centrilobular hepatocytes at 100 and 1000 ppm. **The LOAEL is 100 ppm (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. The NOAEL is 5 ppm (0.5 mg/kg/day).**

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirements (OPPTS 870.3100; OECD 408) for a 90-day toxicity study in rats.

00103014 Kalinowski AE, Chalmers DT, Chart IS, et al. (1981) PP021: 26 week oral dosing
study in dog. Central Toxicology Laboratory (Alderley Park, Cheshire, UK). Laboratory Report No. CTL/P/591, March 5, 1981. Unpublished.

EXECUTIVE SUMMARY - In a 26-week oral toxicity study (MRID 00103014), fomesafen (97.5% a.i., batch #Y00053/001/005) was administered to 6 Beagle dogs/sex/dose in gelatin capsules at dose levels of 0, 0.1, 1, or 25 mg/kg bw/day. There were no treatment-related effects on survival, clinical parameters, body weight, or food consumption. Mean hemoglobin concentrations and erythrocyte counts were slightly decreased in both sexes combined (6-10%), relative to controls, at 25 mg/kg from weeks 4-20. Mean hematocrit was also slightly decreased (6-9%), relative to controls, in both sexes combined at 25 mg/kg during the same period. At 25 mg/kg in both sexes combined, mean platelet counts increased by 10-23% from week 8-20,

while from weeks 4-16 mean prothrombin time was increased only slightly (3-4%), relative to controls. Taken together, these results are suggestive of slight anemia at 25 mg/kg.

Mean absolute and relative liver weights were increased in males by 10% and 13%, respectively, at 25 mg/kg. The slight increase in liver weights in males was regarded as non-adverse. The adaptive nature of the liver changes was also supported by a 19% (males) and 15% (females) increase in smooth endoplasmic reticulum (SER), indicative of increased protein synthesis. Mean plasma cholesterol levels were decreased by 31-40%, relative to controls, in both sexes combined from weeks 1-26, while mean plasma triglycerides were decreased by 45-56% over the same period. A 3- and 2-fold increase, relative to controls, in the mean number of peroxisomes in centrilobular hepatocytes was also observed in males and females, respectively, at 25 mg/kg. Peroxisome proliferation is an adaptive response to hypolipidemic compounds. Changes in the "tinctorial properties of hepatocytes" was also observed in 4/6 males and 4/6 females at 25 mg/kg; these changes in staining reflect the observed changes at the organelle level, i.e., increase in peroxisome number and SER, and while treatment-related, are considered non-adverse.

The LOAEL is 25 mg/kg bw/day, based on hematology (decreased hemoglobin and hematocrit concentrations and erythrocyte count and increased platelet count and prothrombin time). The NOAEL is 1 mg/kg bw/day.

This chronic oral toxicity study in the dog is **Acceptable/Guideline** and satisfies the guideline requirements for a chronic oral toxicity study in non-rodents (OPPTS 870.4100; OECD 452).

00103016 Wickeramaratne, G.A., Richards, D., Babham, P.B. (1982) Fomesafen: Teratogenicity study in the rat. CTL/P/656 and CTL/P/656S prepared by Central Toxicology Laboratory, Imperial Chemical Industries PLC, Alderley Park, Macclesfield, Cheshire, UK. Unpublished Study.

EXECUTIVE SUMMARY - In a developmental toxicity study (MRID 00103016), Fomesafen (97.5% a.i.) was administered to 19-21 pregnant rats/dose in corn oil by gavage at dose levels of 0, 1.0, 7.5 or 50 mg/kg bw/day from days 6 through 15 of gestation.

There was no maternal and/or fetal toxicity evident at any dose level tested. However, this study should be considered with: 1) Report No. CTL/P/576, MRID #00164903, and 2) information provided by Syngenta in their submission (DP 316263, MRID 46527208) in establishing the NOAEL and LOAEL (see Discussion/Added Information Section). With the additional information, the following conclusions can be made. **The maternal LOAEL is 200 mg/kg bw/day, based on staining of the ventral fur and significantly decreased body weight gain (>10%). The maternal toxicity NOAEL is 100 mg/kg bw/day. The developmental LOAEL is 200 mg/kg bw/day based on postimplantation loss observed in study CTL/P/576 (MRID 00164903). The developmental NOAEL is 100 mg/kg bw/day.**

This developmental toxicity study is classified **Acceptable/Guideline** and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rat in combination with another developmental toxicity in rat (CTL/P/576, MRID 00164903).

00109214 Wickeramaratne, G. A., Richards, D., Imartin, M., Doss, A., Ishmail, J., Taylor, D., Forbes, D., smf Godley, W.J. PP021: Teratogenicity Study in the Rabbit. Unpublished Report No. CTL/P/578. Central Toxicology Laboratory, Imperial Chemical Industries PLC, Alderley Park, Macclesfield, Cheshire, UK. Unpublished.

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 00109214), fomesafen (97.5% a.i.) was administered to at least 13 pregnant Dutch rabbits/group orally (in gelatin capsules) at dose levels of 0, 2.5, 10, or 40 mg/kg/day from days 6 through 18 of gestation. Due to the low number of pregnant does in the low and high dose groups after the initial mating, 6 mated rabbits were added to the control, low, and mid dose groups and 7 to the high dose group. The remaining does were sacrificed on GD 29; their fetuses were removed by cesarean section and examined. A total of 17 animals died on study. Total mortality (including sacrifice *in extremis*) was 3/24, 3/24, 4/24, and 7/25 at 0, 2.5, 10, and 40 mg/kg/day, respectively. The incidence of mucous around the nose and/or forepaws increased in a dose-dependent manner: 3/24, 3/24, 4/24 and 8/25 at 0, 2.5, 10 and 40 mg/kg/day, respectively. Pasteurella multocida was isolated from two animals found dead or removed from the study prior to GD 29. However, no other animal was tested for infection with Pasteurella multocida. In the high dose group only, 6/25 does appeared thin, although body weight gain was not affected overall. Mean food consumption was 34% higher ($p<0.05$) than controls in the 40 mg/kg/day group during days 20-29. An increased incidence (6/25) of erosion of the stomach (hemorrhagic foci) was observed macroscopically in high dose females versus 1/24 in controls, 2/24 at 2.5 mg/kg/day, and 0/24 at 10 mg/kg/day. Erosion of the stomach was also observed in a separate, preliminary study at 75 and 150 mg/kg/day with an incidence of 7/12 animals at each dose.

The maternal LOAEL was unable to be determined due to the occurrence of an apparent bacterial infection in the animal colony.

There was no significant difference between the control and treated groups in pregnancy rate or abortions. While the mean number of implantations/dam was similar across dose, the number of corpora lutea/dam was significantly ($p<0.05$) increased in the high dose group (10.6) relative to controls (7.7). This resulted in an increase in pre-implantation loss at the high dose only. This observation was not considered toxicologically significant, because it suggested that dosing took place before the completion of implantation, resulting in maternal-stress-induced embryo lethality. Early and late fetal deaths increased in the mid-dose group only (7/24, 3/24, respectively) relative to controls (4/24, 1/24, respectively). There was an increased frequency of partially ossified hyoid (7.1%) and right vestigial rib (#13, 5.4%) at 40 mg/kg/day relative to controls (2.9 and 0%, respectively). However, these variants are not regarded as toxicologically significant.

The developmental LOAEL was unable to be determined due to the occurrence of an apparent bacterial infection in the animal colony.

Because of an apparent bacterial infection in the animal colony; individual animal data were not reported; all fetuses were not examined for both soft tissue and skeletal alterations; and historical control data were not provided, the developmental toxicity study in the rabbit is classified **Unacceptable/guideline**. This study does not satisfy the guideline requirement for a developmental toxicity study [OPPTS 870.3700; §83-3(b)] in the rabbit.

00131491 Colley, J.; Slater, N.; Heywood, R.; et al. (1983) Fomesafen: 2- Year Feeding Study in Mice: HRC Report No. ICI 318/82754; Sponsor's Study No. PM 0386; CTL/C/1207A through E. Final rept. (Unpublished study received Oct 13, 1983 under 10182-EX-33; pre- pared by Huntingdon Research Centre, Eng., submitted by ICI Americas, Inc., Wilmington, DE; CDL:071999-A; 072000; 072001). Unpublished.

EXECUTIVE SUMMARY: In a chronic feeding/oncogenicity study (MRID 00131491), Fomesafen (Batch No. P28 and ICI Part No. Y00053/001/007, 97.2%) was administered in the diet to CD-1 mice (52/sex/group; control group contained 104 mice/sex) for up to 104 weeks at doses of 0, 1, 10, 100 or 1000 ppm (equivalent to 0, 0.15, 1.5, 1.5 or 15 mg/kg/day). An interim sacrifice was scheduled at 52 weeks utilizing additional groups of 12 mice/sex, except for the control group which contained 24 mice/sex.

Male mice in the 1000 ppm group were terminated after 80 treatment weeks (80% survival) and female mice were terminated after 90 treatment weeks (70% survival). No significant increases in mortality were observed at the lower treatment doses. There was a high incidence of male and female mice with swollen abdomens in the 1000 ppm group by terminal sacrifice.

Erythrocyte counts, hemoglobin levels and hematocrits were decreased in male and female mice in the 1000 ppm group at terminal sacrifice. AP and GPT activities were significantly increased in males females in the 100 and 1000 ppm groups at 52 weeks. Liver weights and liver-to-body weight ratios were significantly increased in both sexes receiving 100 and 1000 ppm Fomesafen. Kidney, adrenal, and heart weights were significantly increased at 1000 ppm. Because the organ-to-body weight ratios were not significantly different from the controls, fomesafen. was not considered to have a significant toxicological affect on these organ weights. The incidence of liver masses was significantly increased in males receiving 1, 100 and 1000 ppm fomesafen and in females receiving 100 and 1000 ppm fomesafen. The increase in liver masses was accompanied by increases in enlarged and discolored livers and by increases in eosinophilic hepatocytes and pigmented macrophages and/or Kupffer cells. The incidence of malignant liver cell tumors was significantly ($p< 0.001$) increased in. males and females receiving 1000 ppm fomesafen. **The LOAEL is 100 ppm (equivalent to 1.5 mg/kg/day) based on the presence of liver tumors and liver weight increases in male and female mice. The NOAEL is 10 ppm (equivalent to 0.15 mg/kg/day).**
The submitted study is classified as **Acceptable/Guideline** and does satisfy the requirements for a chronic feeding/oncogenicity study in mice (OPPTS 870.4300; OECD 453).

00135632 Henderson, C., Parkinson, G., Oliver, G., et al. (1983) Subacute Dermal Toxicity in Rabbits. Imperial Chemical Industries, PLC Central Toxicology Laboratory, UK. Laboratory Report Number CTL/P/555, March 15, 1983. Unpublished.

EXECUTIVE SUMMARY - In a 21-day dermal toxicity study (MRID 00135632), fomesafen (90.8% a.i.; Batch/Lot # P 21 C4915/26/1) in propylene glycol suspension was applied to shaved intact or abraded skin of New Zealand white rabbits (10/sex/dose; 5 intact and 5 abraded skin/sex) at dose levels of 0, 10, 100, or 1000 mg/kg bw/day (limit dose), 6 hours/day, 5 days/week for 3 weeks.

No treatment-related effects were observed on mortality, body weight, body weight gain, food consumption, hematology, clinical chemistry and urinalysis at any dose in either sex. Clinical signs (subdued behavior) was observed only in the high-dose animals immediately after the application of test material. Clinical signs in the high-dose group were not considered as toxicologically significant since they were observed immediately after treatment. A slight reduction in food consumption and an increase in thyroid weight were also observed. However, these effects were not considered treatment-related, since there was no dose response.

Fomesafen produced moderate to severe skin reactions manifested as erythema, edema, scaling and crust in the treated area in the 100 and 1000 mg/kg/day dose groups.

The systemic toxicity LOAEL was not observed in this study. The systemic toxicity NOAEL is 1000 mg/kg/day (limit dose).

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3200; OECD 410) for a 21-day dermal toxicity study in rats.

00142125 Milburn, G., Banham, et al. (1984) Fomesafen: 2 year feeding in rats: Report no. CTL/P/863. Unpublished study prepared by ICI Americas, Inc. 550p. Unpublished.

EXECUTIVE SUMMARY - In this combined chronic toxicity/carcinogenicity study (MRID 00142125), Fomesafen (97.5% a.i.; CTL Reference No. Y00053/001; Batch No. P28) was administered in the diet for 2 years to 52 Wistar albino rats/sex/dose at doses of 0, 5, 100 or 1000 ppm (equivalent to 0, 0.25, 5 and 50 mg/kg/day). In addition, groups of 12 rats/sex received the same dietary concentrations for up to 52 weeks (interim sacrifice).The actual concentrations of fomesafen in the test diets were in the acceptable range of 10% of the nominal concentrations.

There was an increased incidence of coat staining in males treated with 100 and 1000 ppm fomesafen and in all females treated with fomesafen. Body weights were significantly decreased in males in the 1000 ppm group from weeks 3 through 76. Decreased food utilization efficiencies were observed in males treated with 100 and 1000 ppm fomesafen during the first 14 weeks of the study. Significant increases in the activities of plasma alkaline phosphatase, alanine

transaminase and aspartate transaminase, and in plasma albumin were observed in male rats

treated with 1000 ppm fomesafen. Significant reductions in plasma cholesterol and triglycerides

were observed in males and females treated with 1000 ppm fomesafen. Male and female rats treated with 1000 ppm fomesafen had depressed protein excretion in urine. Mean liver weights were significantly increased in males and females administered 1000 ppm fomesafen in the diet. Hyalinization of the liver was observed in rats administered 100 and 1000 ppm fomesafen in the diet. Biliary hyperplasia, bile duct dilatation and portal fibrosis were decreased in groups treated with 1000 ppm fomesafen. Pigmentation of portal macrophages, Kupffer cells, and hepatocytes was substantially increased in males and slightly increased in females treated with 1000 ppm fomesafen. **The LOAEL is 100 ppm (5 mg/kg/day), based on hyalinization of the liver in males. The NOAEL is 5 ppm (0.25 mg/kg/day).**

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirements (OPPTS 870.4300; OECD 453) for a combined chronic toxicity/carcinogenicity study in rats.

00144862 Tenston, D.J. et al (1984) Fomesafen: Two-Generation Reproduction Study in the Rat. Central Toxicology Laboratory, Imperial Chemical Industries PLC, Alderley Park, Macclesfield, Cheshire, UK. Study number RR0199, 1984. Unpublished.

EXECUTIVE SUMMARY - In a two-generation reproduction toxicity study (MRID 00144862) Fomesafen (P28; 97.5% a.i.) was administered in diet to 30 Wistar rats (Alderley Park-derived)/sex/dose at dose levels of 0, 50, 250, or 1000 ppm (equivalent to 0, 2.5, 12.5, or 50 mg/kg/day) , for 2 generations. The F_1A pups were weaned on postnatal day (PND)22 and F_1B, F_2B and F_2A pups were weaned PND 29. Thirty F_1B females and 15 males were selected to become F_1 parents and produced F_2B litters. Brother-sister matings were avoided in each parental generation.

In the parental animals, no treatment-related effects were observed on body weights, or food consumption.

At 1000 ppm, an increased incidence of liver alterations were seen male and female F_0 and F_1 parents. These include congestion (M & F), multifocal necrosis (M), Kupffer cell pigmentation (M), hyalinization (diffuse and centrilobular; M & F) and biliary hyperplasia (M & F). An increased incidence of liver hyalinization was observed in the livers of F_1b males, however, these effects are considered to be of systemic effect rather than offspring toxicity. No liver alteration were observed at 250 ppm.

The parental LOAEL = 1000 ppm (50 mg/kg bw/day), based on liver histopathology in males and females of both generations. The maternal toxicity NOAEL = 250 ppm (12.5 mg/kg bw/day).

An increased incidence of liver hyalinization was observed in the livers of F_1b male pups. [Although, representative samples of liver from pups in the mid- and low-dose groups were not microscopically examined, hyalinization would not be expected to be observed since it was not observed in the livers of the parental animals in the low- and mid-dose groups.]

The offspring LOAEL = 1000 ppm (50 mg/kg/day), based on increased incidence of liver hyalinization in males. The offspring NOAEL = 250 ppm (12.5 mg/kg bw/day).

No treatment-related reproductive parameters were affected due to treatment with fomesafen. Reductions of litter size (15 - 20%) was observed in $F_1$and F_2 A litter at 250 ppm. A significant reduction 20% in litter size was observed at 1000 ppm F_2B litters, however, there was no reduction in litter sizes in other 3 1000 ppm groups. A 13% reduction in litter size was also observed at 50 ppm in F_1 B litters. These litter reductions were sporadic, not dose-related, and therefore, considered to be of no toxicological significance. At 1000 ppm, an increased incidence of hyalinization of the liver was observed in F1B pups in the 1000 ppm group.

The reproductive NOAEL = 1000 ppm (50 mg/kg/day). The LOAEL was not established.

The study is classified **Acceptable/Guideline** and satisfies the guideline requirement for a reproduction toxicity (OPPTS 870.3800; OECD 416) for a two-generation reproduction study in the rat.

00164903 Wickeramaratne, G.A., Richards, D., Babham, P.B. (1981) PP021: Teratogenicity study in the rat. CTL/P/576 and CTL/P/567S prepared by Central Toxicology Laboratory, Imperial Chemical Industries PLC, Alderley Park, Macclesfield, Cheshire, UK. Unpublished.

EXECUTIVE SUMMARY - In a developmental toxicity study (MRID 00164903), Fomesafen (97.5% a.i.) was administered to 17-24 pregnant rats/dose in corn oil by gavage at dose levels of 0, 50, 100 or 200 mg/kg bw/day from days 6 through 15 of gestation.

Maternal toxicity was evident at dose of 200 mg/kg bw/day (the highest dose tested) and was associated with staining of the ventral fur in 15 of 20 animals and significantly decreased body weight gain (>10%) during the dosing period (Days 7-16; Days16-21). Food consumption in the high-dose group was also significantly decreased as compared to the control group during the dosing period (Days 7-16; Days 16-21).

However, this study should be considered with: 1) Report Nos. CTL/P/656 and CTL/P/656S, MRID #001013016, and 2) information provided by Syngenta in their submission (DP 316263, MRID 46527208) in establishing the NOAEL and LOAEL (see Discussion/Added Information Section). With the additional information, the following conclusions can be made. **The maternal LOAEL is 200 mg/kg bw/day, based on staining of the ventral fur and significantly decreased body weight gain (>10%). The maternal toxicity NOAEL is 100 mg/kg bw/day. The developmental LOAEL is 200 mg/kg bw/day based on postimplantation loss. The developmental NOAEL is 100 mg/kg bw/day.**

This developmental toxicity study is classified **Acceptable/Guideline** and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rat in combination with another developmental toxicity in rat (MRID 001013016).

40786709 Colley, J., Cladee, S., Street, A., Heywood, R., Gibson, W., Prentice, D., Buckley, P., and Offer, J. (1980) Preliminary Assessment of PP 021 Toxicity to Mice by Dietary Administration for 4 weeks. Huntingdon Research Center, Huntingdon, U.K. Study No. ICI/317/80148, September 13, 1980. Unpublished.

EXECUTIVE SUMMARY - In a 28-day range finding oral toxicity study (MRID 40786709), fomesafen (94% a.i., Batch/Lot # P 21 and ICI TSC No. Y00053/001/004) was administered to CD-1 mice (10/sex/dose) in the diet at doses of 0, 5, 15, 50, 150, 500, 1500, or 5000 ppm (equal to 0/0, 0.71/0.94, 2.13/2.87, 7.20/8.30, 20.7/27.1, 68.9/83.4, 209.1/246.8, or 917.2/1247.6 mg/kg/day [M/F]) for up to 28 days.

Clinical signs consisting of emaciation were noted in two females in the high dose group (5000 ppm) and in one female in the 150 ppm dose group. Since there was no dose response, the effect was not considered treatment-related. Mortality was seen in one male at 15 ppm in week 2, one male at 50 ppm during week 4 and one female at 5000 ppm during week 4. Statistically significant decreased body weights and body weight gains were observed in high-dose animals only. Food efficiency was also decreased in high-dose animals only. Clinical chemistry parameters were not evaluated in this study. A slight decrease in erythrocytes, hemoglobin, mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) was observed in high- dose females, while decreased MCH and a slight increase in erythrocytes were seen in high-dose males. These changes in hematological parameters were indicative of slight anemia and were therefore regarded as toxicologically significant. Statistically significant increases in liver weights were observed in males at $\geq$50 ppm and in females at $\geq$150 ppm. Enlarged hepatocytes were also observed. However, since there were no corroborating adverse histopathological findings, these effects were considered adaptive changes. All high-dose animals exhibited bile duct hyperplasia. Small seminal vesicles were observed in 2/10 high-dose males, while small uteri were observed in 4/10 females at 1500 ppm and in 9/10 high-dose females.

Under the conditions of this study, the LOAEL was 5000 ppm (equal to 917/1247 mg/kg/day in M/F) based on decreased body weights and body weight gains, decreased food efficiency, hematology (decreased erythrocyte count, hemoglobin, mean corpuscular volume, and mean corpuscular hemoglobin), bile duct hyperplasia, decreased uterine size in females, and decreased size of the seminal vesicles in males. The NOAEL is 1500 ppm (equal to 209/247 mg/kg/day in M/F).

This 28-day oral study is **acceptable/non-guideline**, because treatment was less than 90 days (or 10% of the animal's lifespan), as required by Guideline OPPTS 870.3100 for a subchronic oral toxicity study in rodents.

44569805 Howard, C.A., Richardson, C.R. (1989) Fomesafen: An evaluation in the *in vitro* cytogenetic assay in human lymphocytes. Central Toxicology Laboratory, Alderley Park, Macclecsfield, Cheshire, UK SK104TJ. Laboratory Project ID: CTL/P/2378, April 4, 1988. Unpublished.

EXECUTIVE SUMMARY: In a mammalian cell cytogenetics assay (chromosomal aberrations) (MRID 44569805), human lymphocytes (obtained from one male and one female

donor) in culture were exposed to fomesafen (96.7% a.i.) in dimethyl sulfoxide (DMSO) at concentrations of 0, 150, 500, and 1000 ug/ml in the absence of S9-mix and 75, 150, and 250 ug/ml in the presence of S9 mix for 3-3.5 hours and harvested 72 hours after the beginning of treatment. Two-hundred cells (100 per duplicate coded slide) were evaluated for metaphases with structural aberrations. The S9-fraction was obtained from Aroclor 1254 induced male Sprague Dawley rat liver.

Fomesafen was tested at concentrations ranging from 150-1000 ug/mL (−S9) and 75-250 ug/mL (+S9). A significant increase in chromosome fragments was observed in lymphocytes from donor 1 at 1000 ug/mL (−S9). However, the clastogenic response is most likely secondary to cytotoxicity as the MI was reduced by 57% in these cells. In the repeat experiment (−S9, donor 1), the MI decreased by 56% and clastogenicity was not observed. Proper experimental protocol was followed and the solvent and positive control values were appropriate. **There was no evidence of chromosome aberrations induced over background.**

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirement for Test Guideline OPPTS 870.5375; OECD 473 for *in vitro* cytogenetic mutagenicity data.

44569806 Mellano, D., Berruto, G. (1984) Fomesafen: In vitro study of chromosome aberration induced by fomesafen in cultured human lymphocytes. Istituto Di Ricerche Biomediche, "Antoine Marxer" S.p.A., Casella Postale 226, 10015 Ivrea. Laboratory Project ID: CTL/C/1262, May 16, 1984. Unpublished

EXECUTIVE SUMMARY: In an *in vitro* mammalian cell cytogenetics assay (Chromosomal aberrations) (MRID 44569806), human lymphocytes (obtained from 1 male donor) in culture were exposed to fomesafen (97.5% a.i.) in dimethyl sulfoxide (DMSO) at concentrations of 0, 10, 100, and 1000 ug/ml in the absence and presence of metabolic activation for 3 hours and harvested 26 hours after the beginning of treatment. One-hundred cells (duplicate slides) were evaluated for metaphases with structural aberrations. The S9-fraction was obtained from Aroclor 1254 induced male Sprague Dawley rat liver.

Fomesafen was tested up to a cytotoxic concentration for this assay. Cytotoxicity was observed at 1000 ug/ml with and without S-9 mix. No statistically or biologically significant increases in chromosomal damage were observed at any of the dose levels either in the presence or absence of metabolic activation. The solvent and positive controls induced the appropriate response. **There was no evidence of chromosome aberrations induced over background.**

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirement for Test Guideline OPPTS 870.5375; OECD 473 for *in vitro* cytogenetic mutagenicity data.

Appendix 2. Proposed Tolerances/Tolerance Reassessment

Tolerances for fomesafen residues are listed in 40 CFR §180.433. Currently, the single established tolerance is expressed in terms of "sodium salt of fomesafen, 5-[2-chloro-4-(trifluoromethyl)phenoxy]-*N*-(methylsulfonyl)-2-nitrobenzamide." HED has determined that the residue of concern for tolerance expression is fomesafen. Therefore, the established tolerance expression should be revised to be expressed in terms of fomesafen *per se*, by removing the phrase "sodium salt of" from 40 CFR §180.433(a).

The available crop field trial data and revised analytical method will support the proposed revised tolerance for soybean seed at 0.02 ppm. The data for soybean aspirated grain fractions indicate that a tolerance is required for this commodity, at 0.05 ppm. The available crop field trial data for cotton, dry beans and snap beans indicate that the proposed tolerances of 0.025 ppm for residues of fomesafen *per se* in/on cotton seed, cotton byproducts, dry beans and snap beans are appropriate. For snap bean, the proposed tolerance was expressed in terms of fomesafen sodium; the tolerance expression should be revised to fomesafen *per se*.

The registrant's most recent Reflex® Herbicide label reflects regional use of fomesafen on the commodities listed above, however, the residue chemistry data submitted in support of this action are of sufficient geographic representation to support full U.S. registration; therefore, HED recommends that these tolerances be listed in the general section of 40CFR 180.433. A summary of the tolerance reassessment for fomesafen sodium is presented in Table 9. The proposed tolerances should be revised to reflect the correct commodity definitions as specified in Table 9.

Table 9. Tolerance Reassessment Summary for Fomesafen Sodium.

Commodity	Current/Proposed Tolerance (ppm)	Range of Residues (ppm)	Tolerance Reassessment (ppm)	Comment/*[Correct Commodity Definition]*
Tolerances Listed Under 40 CFR §180.433(a):				
Soybean	0.05/0.02 [1]	<0.02	0.02	*Soybean, seed*
Proposed Tolerances, to Be Listed Under 40 CFR §180.433(a):				
Cotton seed	0.025 [2]	<0.025-0.0311	0.025	*Cotton, undelinted seed*
Cotton gin byproducts	0.025 [2]	≤0.02	0.025	*Cotton, gin byproducts*
Dry bean	0.025 [2]	<0.025	0.025	*Bean, dry*
Snap bean	0.025 [3]	<0.02, <0.025	0.025	*Bean, snap, succulent*
Tolerances to be Proposed, under 40 CFR 180.433(a):				
Soybean, aspirated grain fractions	--	<0.02-0.041	0.05	

[1] The current tolerance, for residues of the sodium salt of fomesafen, is 0.05 ppm. Syngenta has requested a lower tolerance of 0.02 ppm.
[2] Tolerance proposed for residues of fomesafen *per se*.
[3] Tolerance proposed for residues of the sodium salt of fomesafen.