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MEMORANDUM

Date: February 19, 2010

SUBJECT: **Fomesafen Sodium:** Human Health Risk Assessment for the Establishment of Tolerances and Registration of New Uses of Fomesafen Sodium on Potatoes and Tomatoes.

PC Code: 123802
Decision No.: 409397
Petition No.: 9F7563
Risk Assessment Type: Human Health Risk Assessment
TXR No.: NA
MRID No.: NA

DP Barcode: D373963
Registration No.: 100-993
Regulatory Action: New Use/Tolerance
Case No.: NA

CAS No.: 72178-02-0
40 CFR: §180.433

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This document provides the Health Effects Division (HED) human health risk assessment for the proposed establishment of tolerances and registration of the new uses of herbicide fomesafen sodium on potatoes and tomatoes.

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1.0 Executive Summary

The Health Effects Division (HED) has conducted a human health risk assessment for the active ingredient fomesafen 5-[2-chloro-4-(trifluoromethyl)phenoxy]-N-(methylsulfonyl)-2-nitrobenzamide) for the purpose of establishing a tolerance and registering a new use on potatoes and tomatoes. Fomesafen sodium is an herbicide used for 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. There are no residential uses for fomesafen. Reflex® Herbicide (22.8% active ingredient sodium salt of fomesafen) is applied at a maximum rate of 1 pt of product per acre (0.25 lb ae/A) on potatoes and at a maximum rate of 1.5 pt of product per acre (0.375 lb ae/A) on transplanted tomatoes. The product is applied to potatoes as a broadcast pre-emergence application after planting but before potato emergence for control of weeds; the product is applied to transplanted tomatoes as a pre-plant non-incorporated pre-emergence broadcast applications up to seven days prior to transplanting tomatoes for control of weeds.

Hazard Characterization

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 show signs of neurotoxicity. 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. Immunotoxicity, acute neurotoxicity, and subchronic neurotoxicity studies are now required.

There was no evidence of increased susceptibility of fetuses or offspring in developmental or reproductive toxicity studies and the FQPA safety factor was reduced to 1X.

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 point of departure used to establish the chronic population adjusted dose (cPAD) was microscopic liver changes in the chronic toxicity study in rats. An endpoint for incidental oral exposure (short and intermediate term) for infants and children was microscopic liver changes, increased liver weights in males and females, and increases in liver enzymes in a 90-day study in rats.

The endpoint to assess short- and intermediate-term dermal risk was postimplantation loss and decreased maternal body weight gain in the developmental toxicity study in rats. A dermal absorption value of 20% (based on dermal absorption factors for similarly structured compounds) was applied. The endpoint to assess long-term dermal and inhalation risk was microscopic liver changes in the chronic toxicity study in rats.

The endpoint to assess short and intermediate term inhalation exposure was microscopic liver changes, increased liver weights in males and females, and increases in liver enzymes in a 90-day study in rats.

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

Residue Data

Sufficient residue data are available to support the proposed tolerance in/on tomatoes. The residue of concern is only the parent, fomesafen. Crop metabolism data are not available to support the proposed tolerance in/on potatoes. A root and tuber metabolism study is needed before HED can recommend for a tolerance. The residue data are supported by adequate storage stability data and an analytical method is available to support the proposed tolerance in/on tomatoes.

Dietary Exposure and Risk

The environmental fate data indicated that fomesafen is likely to be persistent and mobile in aquatic and terrestrial environments. EFED has calculated estimated drinking water concentrations (EDWCs) 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 ppb for surface water EDWCs; since the prospective groundwater monitoring concentration of 1.0 ppb is lower than the surface water value, dietary assessment using the surface water residue will be protective for 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.

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 unrefined assessments were tolerance level residues and 100% crop treated. Estimated drinking water concentrations (EDWCs) from the Environmental Fate and Effects Division were also included. The dietary exposure analyses in this assessment result in dietary risk estimates for food and water that are below the Agency's level of concern for chronic dietary exposure for all population groups. The subgroup with the highest exposure and risk estimates is infants. The exposure for food plus surface water was 0.000791 mg/kg/day, which is 32% of the chronic population adjusted dose (cPAD) (D372850, C. Olinger, 1/21/2010).

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

Aggregate Risk Assessment

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.

Since no acute endpoint was selected, a quantitative acute assessment is not required. Since there are no residential uses for fomesafen, the chronic aggregate risk assessment would combine food and water only. As described above, the chronic dietary assessment is below the level of concern.

Occupational Risk Assessment

There is potential for occupational exposure to fomesafen during mixing, loading, and application activities; therefore, short- and intermediate-term worker exposure and risk assessments were conducted. 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 and 10X for interspecies variability. 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 different. Occupational exposure was evaluated by following Exposure Science Advisory Council SOPs and data from the Pesticide Handlers Exposure Database (PHED). Data from adult human subjects in the PHED study has received ethical review and all regulatory requirements were met.

Occupational Handler Risk: Occupational dermal and inhalation daily dose values were calculated and presented. For occupational handlers, dermal and inhalation MOEs above 100 are not of concern. All occupational exposure risk estimates for Reflex®, for short- and intermediate- term exposures for handlers, are not of concern with single layer dermal Personal Protective Equipment (PPE) (includes long-sleeve shirt, long pants, gloves) or with engineering control enclosed cab (fixed wing aircraft). Dermal MOEs ranged from 12,000 to 130,000 and inhalation MOEs ranged from 220 to 5,900.

Occupational Post-application Risk: As the herbicide is applied pre-emergence for potato and tomato crops, no occupational post-application exposures are expected.

Human Studies: This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies, which comprise the Pesticide Handlers Exposure Database (PHED), have been determined to require a review of their ethical conduct, have received that review, and are considered ethically and scientifically acceptable for use in risk assessment.

Regulatory Recommendations

Pending resolution of the deficiency pertaining to directions for use, there are no residue chemistry issues that would preclude granting a conditional registration for the use of sodium fomesafen on tomatoes and establishing a tolerances for fomesafen in/on tomatoes at 0.025 ppm. Confined rotational crops studies should be required as a condition of registration.

At this time, data are not available to support rotation to other crops beyond those commodities that are currently registered and proposed as primary crops; therefore, the petitioner must revise the Reflex® Herbicide label to permit immediate replanting of soybeans, cotton, dry beans, snap beans, and tomatoes only (phytotoxicity concerns permitting) with a restriction that other crops can only be planted 12 months after treatment or 18 months after treatment if based on phytotoxicity concerns.

The registrant's most recent Reflex® Herbicide label reflects regional use of fomesafen on tomatoes. 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 40 CFR §180.433.

Note to PM: According to HED's Interim Guidance on Tolerance Expressions (5/27/09, S. Knizner), the tolerance expression for fomesafen should be revised to state:

> "Tolerances are established for residues of fomesafen, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only fomesafen [5-[2-chloro-4-(trifluoromethyl)phenoxy]-*N*-(methylsulfonyl)-2-nitrobenzamide]."

HED cannot recommend for the requested tolerance in/on potatoes due to the lack of an adequate root/tuber metabolism study.

Label Recommendations

The proposed label should be revised to remove the use on potatoes based on lack of an adequate root/tuber metabolism study. The label should be revised to permit immediate replanting of soybeans, cotton, dry beans, snap beans, and tomatoes only (phytotoxicity concerns permitting) with a restriction that other crops can only be planted 12 months after treatment or 18 months after treatment if based on phytotoxicity concerns.

The label should be revised to remove the requirement of use of a respirator for mixer/loaders in support of aerial application handling more than 140 gallons of product per day. This requirement is not enforceable and should be removed from the label since there is no viable system in place for inspectors to validate daily use patterns for applicators that would ensure this requirement is properly implemented.

According to the label, applications are not to be made through any type of irrigation equipment except center pivot systems. The PM should note that there are other permanent systems outside of center pivot irrigation equipment which are essentially culturally equivalent (e.g. drip irrigation systems for tomatoes in raised bed culture).

2.0 Ingredient Profile

2.1 Summary of Registered and Proposed Uses

Background on Currently Registered Use Pattern: Fomesafen (5-[2-chloro-4-(trifluoromethyl)phenoxy]-N-(methylsulfonyl)-2-nitrobenzamide) is a selective herbicide which may be applied pre-plant, pre-emergence, and/or postemergence for control and suppression of broadleaf weeds, grasses, and sedges. Fomesafen sodium is a contact herbicide for control of broadleaf weeds. Fomesafen is currently registered for pre-plant, pre-emergence and early postemergence use on cotton, dry beans and soybeans. There are no residential uses of fomesafen. The existing labels allow ground and aerial application. 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.

Summary of Proposed New Use Pattern: A human health risk assessment has been conducted for the active ingredient fomesafen 5-[2-chloro-4-(trifluoromethyl)phenoxy]-N-(methylsulfonyl)-2-nitrobenzamide) for the purpose of registering a new use on potatoes and tomatoes. Reflex® Herbicide (22.8% active ingredient sodium salt of fomesafen) will be applied at a maximum rate of 1 pt of product per acre (0.25 lb ae/A) on potatoes and at a maximum rate of 1.5 pt. of product per acre (0.375 lb ae/A) on transplanted tomatoes. The product is applied to potatoes as a broadcast pre-emergence application after planting but before potato emergence for control of weeds; the product is applied to transplanted tomatoes as a pre-plant non-incorporated pre-emergence broadcast applications up to seven days prior to transplanting tomatoes for control of weeds. The current label for Reflex® Herbicide, the sole label proposed for amendment in this action, specifies a 24- hr reentry interval for workers.

The draft label specifies that use is restricted to the eastern half of the U.S. Syngenta's regional use map for Reflex® is subdivided into five regions. Reflex® may be applied at a maximum of 0.375 lb ae/A per 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.

Spray additives: The draft label specifies that spray additives cleared for use on growing crops under 40 CFR §180.1001 may be used in the spray mixture. A nonionic surfactant (NIS), crop oil concentrates (COC), or other adjuvants may be used for postemergence applications only. Since the proposed uses on potatoes and tomatoes are either pre-emergence or pre-transplant, the use of surfactants is not needed when Reflex® is applied to these crops.

Application equipment: Ground applications are to be made in a minimum of 10 gal/A, and aerial applications are to be made in a minimum of 5 gal/A. Applications are not to be made through any type of irrigation equipment except center pivot systems. Reflex® alone or in tank mixture with other herbicides on the label, which are registered for center pivot application, may be applied in irrigation water pre-emergence (after planting but before weeds or crop emerge) at label-recommended rates.

Tank mixtures with other products registered for use on potatoes and tomatoes: The draft label provides mixing procedures for tank mixes but does not specify specific tank mix partners for potatoes and tomatoes. The use directions state that, for tank mix combinations, the recommendations, restrictions, and limitations for all products must be followed and that the most restrictive labeling is to apply. For pre-emergence application in potatoes, Reflex® may be tank mixed with other pesticide products *registered* for use in this way and timing in potatoes. For pre-plant non-incorporated pre-emergence applications prior to transplanting tomatoes, Reflex® may also be tank mixed with other pesticide products *registered* for use in this way and timing in tomatoes.

Table 2.1. Use Pattern Summary of Proposed New Use of Fomesafen on Potatoes and Tomatoes

Formulations	Liquid
Pests	Broadleaf weeds, grasses, and sedges
Application Methods	Groundboom; chemigation (center pivot only); fixed-wing aircraft
Application Rates and Intervals	Potato: 1 pt/A (0.25 lb ae/A); Max 1 pt/A/season Tomato: 1.5 pt/A (0.375 lb ae/A); Max 1.5 pt/A/season
Frequency	No minimum rotation interval for potatoes and transplanted tomatoes
Pre-Harvest Interval (PHI)	Potatoes and tomatoes should not be harvested within 70 days after application.
Personal Protective Equipment (PPE)	Applicators and other handlers must wear: long sleeved shirt and long pants, chemical-resistant gloves, shoes plus socks, and protective eyewear. Aerial applications mixers and loaders handling more than 140 gallons of Reflex ® Herbicide in a single workday must wear: dust/must filtering NIOSH-approved respirator

	with any N, R, P or HE filter. (Note: it is recommended that this requirement be removed from the label).
Restricted Entry Interval (REI)	24 hours
Use Directions and Limitations	Potato: Broadcast pre-emergence application after planting but before potato emergence. Refer to Syngenta's Regional Use Map for Reflex® * for determination of maximum use rate that may be applied in each geographic region. Do not apply to any field in Regions 2, 3, 4, or 5 more than once every two years. Do not apply to sweet potatoes or yams. Do not apply as a pre-plant incorporated application as crop injury may occur. Do not apply to emerged potato plants or severe crop injury will occur. Tomato: Broadcast pre-plant non-incorporated pre-emergence application up to 7 days prior to transplanting tomatoes. Refer to Syngenta's Regional Use Map for Reflex® [1] (summarized in the 'General Use Directions' below) for determination of maximum use rate that may be applied in each geographic region. Do not apply to any field in Regions 2, 3, 4, or 5 more than once every two years.

*The draft label 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**.

2.2 Structure and Nomenclature

Tables 2.2a and 2.2b provide structures and nomenclature for fomesafen and sodium salt of fomesafen.

Table 2.2a. Fomesafen Nomenclature.

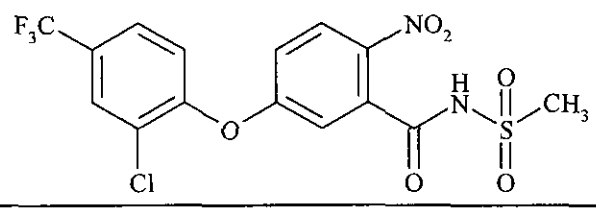
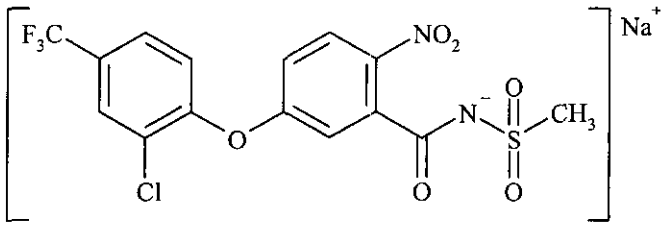
Compound	Chemical Structure
	
Common name	Fomesafen
Company experimental name	N/A
Molecular Formula	$C_{15}H_{10}ClF_3N_2O_6S$
Molecular Weight	438.77
PC code	N/A
IUPAC name	5-(2-chloro-α,α,α-trifluoro-p-tolyloxy)-N-methylsulfonyl-2-nitrobenzamide
CAS name	5-[2-chloro-4-trifluoromethyl)phenoxy]-N-(methylsulfonyl)-2-nitrobenzamide
CAS #	72178-02-0

Table 2.2b. Sodium Salt of Fomesafen Nomenclature.

Table 2.2b. Sodium Salt of Fomesafen Nomenclature.	
Compound	Chemical Structure 
Common name	Sodium Salt of Fomesafen
Company experimental name	N/A
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 #	108731-70-0
End-use product/(EP)	Reflex® Herbicide

2.3 Physical and Chemical Properties

Table 2.3. Physicochemical Properties of Fomesafen.		
Parameter	Value	Reference
Melting point/range	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	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
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 x 10^{-7} mmHg at 50 °C	The Pesticide Manual [1]
Dissociation constant (pKa)	2.7 at 20 °C	
Octanol/water partition coefficient log (K_{ow})	Log K_{OW} = 2.9 at pH 1	
UV/visible absorption spectrum	Not Provided	

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

3.0 Hazard Characterization/Assessment

3.1 Hazard and Dose-Response Characterization

3.1.1 Database Summary

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

3.1.2 Toxicological Effects

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.

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.

3.2 Absorption, Distribution, Metabolism and Excretion

In a metabolism study in rats, fomesafen was readily absorbed in male and female rats after oral dosing. The major route of elimination in females was in the urine whereas in males, it was in the feces, with some enterohepatic recirculation evident. The sex difference was not evident at higher doses where the urine was the main route of excretion for both sexes. At higher doses, the vast majority was excreted unchanged, but at lower doses a lesser amount (60%) was excreted unchanged. The major metabolite (10%) was 5-(2-chloro-α,α,α-trifluoro-tolyloxy)-anthranilic acid. Part, or all, of the metabolism may be due to action by intestinal microorganisms. The rat has a very limited capacity to metabolize fomesafen.

In a metabolism study in dogs, 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. Fomesafen was not extensively metabolized in the dog and was recovered to a large extent unchanged.

3.3 FQPA Considerations

3.3.1 Adequacy of the Toxicity Database

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

An unacceptable developmental toxicity study in rabbits provided information that fomesafen does not pose a hazard to the developing embryo.

3.3.2 Evidence of Neurotoxicity

No neurotoxicity was observed in the studies. Acute and subchronic neurotoxicity studies are now required under 40 CFR Part 158.

3.3.3 Studies Assessing Offspring Sensitivity

Developmental Toxicity Studies in Rats (MRID 00164903)

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.

The maternal LOAEL was 200 mg/kg bw/day, the highest dose tested, based on staining of the ventral fur and significantly decreased body weight gain (>10%). The maternal toxicity NOAEL was 100 mg/kg bw/day. The developmental LOAEL was 200 mg/kg bw/day based on postimplantation loss. The developmental NOAEL was 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).

Developmental Toxicity Study in Rabbits (MRID 00109214)

In a developmental toxicity study (MRID 00109214), fomesafen (97.5% a.i.) was administered to at least 13 pregnant Dutch rabbits/group orally at doses 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.

In the high dose group only, 6/25 does appeared thin, although body weight gain was not affected overall. An increased incidence of erosion of the stomach was observed in high dose females. Mortality due to a bacterial infection was 3/24, 3/24, 4/24, and 7/25 in the respective dose groups. There was no significant difference between the control and treated groups in pregnancy rate or abortions or for developmental abnormalities.

This study provided information to assess potential developmental toxicity rabbits, but was classified unacceptable because of bacterial infection in the colony.

Reproductive Toxicity Study

Rat 2-Generation Reproduction Study (MRID 00144862)

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.

At 1000 ppm, an increased incidence of liver alterations was seen male and female F0 and F1 parents. These include congestion (M & F), multifocal necrosis (M), Kupffer cell pigmentation (M), hyalinization (diffuse and centrilobular; M & F) and biliary hyperplasia (M & F). 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).

The offspring LOAEL = 1000 ppm (50 mg/kg/day), based on increased incidence of liver hyalinization in F1b male pups. The offspring NOAEL = 250 ppm (12.5 mg/kg bw/day).

No treatment-related reproductive parameters were affected due to treatment with fomesafen. The reproductive NOAEL = 1000 ppm (50 mg/kg/day), the highest dose tested.

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.

3.3.4 Degree of Concern Analysis for Pre and Postnatal Susceptibility

There is no evidence of increased susceptibility of rat fetuses to *in utero* exposure to fomesafen. The 2-generation reproduction study in rats did not show evidence of increased susceptibility to fomesafen. Although the developmental toxicity study in rabbits was classified unacceptable due to mortality from bacterial infections, there was adequate information to show that there was not any evidence of increased susceptibility of rabbit fetuses due to the treatment with fomesafen.

Therefore, it is concluded that there is no evidence of increased susceptibility to fomesafen following pre- and/or post-natal exposure and there are no concerns for residual uncertainties for increased susceptibility.

3.4 FQPA Safety Factor for Infants and Children

EPA began requiring functional immunotoxicity testing of all food and non-food use pesticides on December 26, 2007. Since this requirement went into effect after the tolerance petition was submitted, these studies are not yet available for fomesafen. In the absence of specific immunotoxicity studies, the toxicity database was evaluated to determine whether a database uncertainty factor is needed to account for potential immunotoxicity. No evidence of immunotoxicity was found in the database. Due to the lack of evidence of immunotoxicity for fomesafen, it was concluded that a database uncertainty factor is not needed to account for potential immunotoxicity.

EPA began requiring acute and subchronic neurotoxicity studies for all food and non-food use pesticides on December 26, 2007. Since this requirement went into effect after the tolerance

petition was submitted, these studies are not yet available for fomesafen. The toxicity database was evaluated for evidence of neurotoxicity and no evidence for neurotoxicity was found in the database. It was therefore concluded that a database uncertainty factor is not needed to account for potential neurotoxicity.

For the above reasons, and because there are no concerns and/or residual uncertainties for pre- and/or postnatal increased susceptibility, the FQPA safety factor was reduced to 1X.

3.5 Hazard Identification and Toxicity Endpoint Selection

3.5.1 Level of Concern for Margin of Exposure

A summary of the levels of concern for risk assessment may be found in Table 3.5.1. The level of concern (MOEs ≥ 100) is based on 10x for interspecies extrapolation from animals to humans and 10x for variation in sensitivity between humans.

Table 3.5.1. Levels of Concern for Risk Assessment.

Route	Short-Term (1 - 30 Days)	Intermediate-Term (1 - 6 Months)
Occupational (Worker) Exposure		
Dermal	100	100
Inhalation	100	100
Residential Exposure		
Not applicable. There are no residential uses for fomesafen.		

3.5.2 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. Only chronic aggregate risk was assessed since no acute toxicity is likely to result from exposure to fomesafen.

3.5.3 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.

3.5.4 Toxicological Doses and Endpoints

A summary of the hazard endpoints selected may be found in Table 3.5.4.

TABLE 3.5.4 Toxicological Doses and Endpoints for Fomesafen Human Health 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.
Acute Dietary (General US Pop.)	-	-	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
Dermal Short-Term (1 - 30 days) 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 development – rat LOAEL = 200 mg/kg/day based on postimplantation loss
Inhalation Short-Term (1 - 30 days) Intermediate-Term (1 - 6 months)	NOAEL = 0.5 mg/kg/day (Inhalation absorption 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 transminase and aspartate transaminase in males
Long-Term (Dermal & Inhalation)	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
Cancer (oral, dermal, inhalation)	Classification: The CARC classified Fomesafen as "Not Likely to be Carcinogenic to Humans"		

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and 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

* The dermal absorption value of 20% was based on dermal absorption factors for oxyfluorfen and acifluorfen, which have similar structures.

3.6 Endocrine Disruption

As required under FFDCA section 408(p), EPA has developed the Endocrine Disruptor Screening Program (EDSP) to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required

determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Between October 2009 and February 2010, EPA is issuing test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. This list of chemicals was selected based on the potential for human exposure through pathways such as food and water, residential activity, and certain post-application agricultural scenarios. This list should not be construed as a list of known or likely endocrine disruptors.

Fomesafen is not among the group of 58 pesticide active ingredients on the initial list to be screened under the EDSP. Under FFDCA sec. 408(p) the Agency must screen all pesticide chemicals. Accordingly, EPA anticipates issuing future EDSP test orders/data call-ins for all pesticide active ingredients.

For further information on the status of the EDSP, the policies and procedures, the list of 67 chemicals, the test guidelines and the Tier 1 screening battery, please visit our website: http://www.epa.gov/endo/.

In the available toxicity studies on fomesafen, there was no estrogen, androgen, and/or thyroid mediated toxicity.

4.0 Public Health and Pesticide Epidemiology Data

At this time there is no information in the incident reports that affect this risk assessment.

5.0 Dietary Exposure/Risk Characterization

5.1 Residues of Concern

The registrant submitted a new tomato metabolism study in support of this petition that is acceptable and supports the proposed use on tomatoes. The metabolism in tomatoes is submitted to the previously submitted studies on soybeans and cotton. HED generally recommends that three metabolism studies on diverse crops be conducted when a pesticide is to be used on several different commodities. Although three metabolism studies have been submitted, soybeans and cotton are not sufficiently diverse to support the proposed use on potatoes. A potato metabolism study, in which both the root and tops/foliage are analyzed, is required to support the proposed use on potatoes. HED cannot recommend for a tolerance in/on potatoes until an adequate metabolism study is submitted. The residues of concern for food and drinking water are summarized in Table 5.1 below.

Table 5.1. Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	Fomesafen	Fomesafen
Plants	Rotational Crop	Not determined[1]	Not determined[1]
Livestock		Fomesafen, 5-(2-chloro-α,α,α-trifluoro-p-tolyloxy) anthranilic acid, 5-(2-chloro-α,α,α-trifluoro-p-tolyloxy)-N-methylsulfonylanthranilamide.	Not required at this time.[2]
Drinking Water		Fomesafen	NA

[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 finite residues in livestock commodities (180.6 (a)(3)).*

5.2 Residue Profile

5.2.1 Drinking Water Residue Profile

Environmental Fate and Effects Division's (EFED) assessments of potential drinking water impacts from the proposed uses of fomesafen are detailed in the memorandums entitled Tier II Drinking Water Assessment for Fomesafen use on cotton, soybeans, dry beans and snap beans (J. Hetrick, 9/27/2005, D314014) and Drinking Water Assessment for Fomesafen use on cotton, soybeans, dry beans, snap beans, potato and tomato (J. Lin, 12/10/2009, D365204).

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.

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 sediment half-life value. The surface water modeling was conducted on standard EFED scenarios for cotton in TX, NC, MS; soybeans in MS; dry beans and snap beans in IL, MI; potato in ME, FL; tomato in Fl, PA; and nursery crop in FL, TN. 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 maximum application rates of 0.375 lbs ae/A for soybean, dry and snap bean, cotton, and tomato; 0.25 lbs ae/A for potato; and 0.5 lb ae/ A for nursery crop. 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. The scenario leading to the highest EDWC in surface water for chronic exposure (1 in 10 year annual mean concentration) using PRZM-EXAMS was MD cotton, aerial application, with a concentration of 10.535 µg/L (ppb), adjusted for Percent Crop Area (PCA) of 0.87 (D314014). This value was used directly in the dietary exposure assessment.

EFED conducted a ground water assessment using the available environmental fate data and the SCI-GROW model. EFED notes that although the Koc model is inappropriate for estimation of fomesafen soil-water partitioning, the lowest reported Koc 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 (ppb). 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 (ppb), 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 (ppb) 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. Since this value was lower than the surface water EDWC, only the surface water value was incorporated into the dietary assessment.

Surface and ground water estimated drinking water concentrations (EDWCs) for fomesafen are described below:

- The scenario leading to the highest EDWC in **surface water** for chronic exposure (1-in-10 year annual mean concentration) using PRZM-EXAMS was MS cotton, aerial application, with a concentration of 10 ppb, adjusted for a Percent Crop Area (PCA) of 0.87. This value was used directly in the dietary exposure assessment.

- Syngenta submitted a prospective **ground water** monitoring study for fomesafen use on soybeans. EFED recommended using the ground water monitoring concentration of 1 ppb, since it represents actual use conditions of fomesafen on soybeans on a vulnerable soil. Since this value was lower than the surface water EDWC, only the surface water value was incorporated into the assessment.

- The model and its description are available at the EPA internet site: http://www.epa.gov/oppefed1/models/water/.

5.2.2 Food Residue Profile

Twelve crop field trials were submitted in support of the proposed tolerance in/on tomatoes. Residues in all trials were non-detectable at a limit of quantitation of 0.025 ppm. This is consistent with trials on other crops. Processing factors could not be calculated for tomatoes as residues were non-detectable in/on the raw and processed commodities. The metabolism, crop field trial, and processing studies are supported by adequate storage stability studies. The multi-residue methods are not suitable for the analysis of fomesafen. An adequate analytical method is available for the enforcement of tolerances. Syngenta submitted a new LC/MS/MS method (GRM045.01A) for analysis of fomesafen residues, which has been adequately validated in various crop commodities.

Confined rotational crop data remain outstanding. Limited rotational crop field trials reflecting

analysis of only the parent compound are available.

There are no livestock feed items associated with the use on tomatoes. The existing uses of fomesafen result in a 180.6 (a)(3) situation, that there is no reasonable expectation of finite residues and no tolerances in/on livestock commodities are needed.

5.3 Dietary Exposure and Risk

Please see DP Barcode: D372850, Fomesafen Sodium: Chronic Dietary Exposure Assessment to Support Proposed New Use on Tomatoes, January 21, 2010 by Christine Olinger for the complete fomesafen sodium dietary assessment.

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. The analyses were performed to support a proposed new use of fomesafen sodium (commonly called fomesafen) on tomatoes. See Table 5.2 below for a summary of fomesafen chronic dietary exposure risk estimates for food and drinking water.

5.3.1 Acute Dietary Exposure/Risk

No toxic affects attributable to a single dose of fomesafen were found in any study; therefore no acute dietary exposures risks assessment was required.

5.3.2 Chronic (Non-Cancer and Cancer) Dietary Exposure/Risk

Chronic dietary exposure assessments were performed for fomesafen. The assessments resulted in dietary risk estimates for food alone and food and drinking water that are below the HED's level of concern for chronic dietary exposure. For non-cancer exposure, the highest exposure and risk estimates were for all infants (<1 year old), with a cPAD of 32% including food and drinking water.

Table 5.3.2. Summary of Dietary (Food and Drinking Water) Exposure and Risk for Fomesafen.

Population Subgroup	Acute Dietary[1]		Chronic Dietary		Cancer[2]	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD	Dietary Exposure (mg/kg/day)	Risk
General U.S. Population	NA	NA	0.000282	11.3	NA	NA
All Infants (< 1 year old)			0.000791	32		
Children 1-2 years old			0.000480	19		
Children 3-5 years old			0.000441	18		
Children 6-12 years old			0.000302	12		

Youth 13-19 years old			0.000221	8.8		
Adults 20-49 years old			0.000258	10		
Adults 50+ years old			0.000260	10		
Females 13-49 years old			0.000255	10		

[1] No toxic affects attributable to a single dose of fomesafen were found in any study.
[2] Fomesafen classified as "not likely to be carcinogenic".
aPAD = acute population adjusted dose; cPAD = chronic population adjusted dose

5.4 Anticipated Residue and Percent Crop Treated (%CT) Information

Neither anticipated residues nor percent crop treated were used in the dietary assessment.

5.5 Tolerance Assessment

5.5.1 Enforcement Analytical Method

Syngenta Crop Protection has submitted descriptions and validation data for a new proposed enforcement method, Method GRM045.01A, which is entitled "Fomesafen Analytical Method for the Determination of Residues of Fomesafen in Crop Commodities by LC-MS/MS." This high performance liquid chromatography with tandem mass spectrometry detection (LC/MS/MS) method is based on previously submitted gas chromatography with nitrogen phosphorus detection (GC/NPD) methods (refer to DP# 325801, D. Davis, 4/25/06) developed by Zeneca AG.

Method GRM045.01A uses extraction procedures modified from the previous GC/NPD methods. In the revised method, fomesafen residues are extracted with 1% hydrochloric acid in acetonitrile. An aliquot is subjected to an SPE cleanup and analyzed using LC/MS/MS. A second ion transition may be monitored for confirmation. The LOQ is 0.02 ppm for fomesafen in each matrix. Representative spectra and linearity data were submitted demonstrating adequate sensitivity.

Adequate multi-residue method testing data are available, which indicate that the FDA multi-residue methods are not suitable for determining residues of fomesafen.

5.5.2 Tolerance Recommendation

Sufficient residue data are available to support a tolerance of 0.025 ppm in/on tomatoes. Processed commodity tolerances are not needed since detectable residues were not found in either raw or processed tomato commodities.

According to HED's Interim Guidance on Tolerance Expressions (5/27/09, S. Knizner), the tolerance expression for fomesafen should be revised to state:

> "Tolerances are established for residues of fomesafen, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels

specified below is to be determined by measuring only fomesafen [5-[2-chloro-4-(trifluoromethyl)phenoxy]-*N*-(methylsulfonyl)-2-nitrobenzamide]."

5.5.3 International Harmonization

No Codex, Canadian, or Mexican MRLs have been established for residues of fomesafen in/on tomato.

6.0 Residential (Non-Occupational) Exposure

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

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 sodium. 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 database submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift with specific products with significant risks associated with drift.

7.0 Aggregate Risk Assessments

A typical aggregate risk assessment may include residential, food, and drinking water exposure. Because there are no residential uses for fomesafen, the aggregate assessment includes food and drinking water only, as discussed in Section 5.2.

8.0 Occupational Exposure and Risk

This section presents a summary of the occupational exposure and risk estimates for fomesafen. Please see DP Barcode: D373961, Fomesafen Sodium: Occupational Exposure Assessment for a Proposal to Add New Uses on Potatoes and Tomatoes, Alexandra LaMay, February 19, 2010, for the complete fomesafen occupational exposure and risk assessment.

This section describes the occupational exposure and risk assessments conducted to support applications of fomesafen on potatoes and tomatoes. HED determined that the potential for occupational exposure to Reflex® Herbicide exists in a variety of scenarios. The anticipated use patterns indicate several occupational exposure scenarios based on the types of equipment and techniques that can potentially be used for Reflex® Herbicide applications.

8.1 Occupational Handler Exposure

Occupational handler scenarios include handling of Reflex® during mixing, loading, and applying processes. The proposed label states loaders, applicators, and other handlers must wear a long-sleeved shirt, long pants, shoes plus socks and chemical-resistant gloves as personal protective equipment (PPE). Therefore, these scenarios were assessed. Also, for aerial applications, mixers/loaders handling more that 140 gallons of product per day must wear a dust/ mist filtering NIOSH respirator (80% protection factor, PF5) according to the proposed label. For the uses on potatoes and tomatoes, it is assumed that a mixer/loader would not handle more than 140 gallons of product per day; therefore this scenario was not assessed with use of a respirator. However, it is recommended that this requirement be removed from the label as it is not an enforceable requirement.

Short-term and intermediate-term exposures may occur; long term exposures are not expected. Exposure and risk were evaluated using the Pesticide Handlers Exposure Database (PHED).

In this exposure assessment, the use parameters were based on the label instructions and default exposure assumptions for quantity handled per day (ExpoSAC SOPs). The potential absorbed dose and MOEs were calculated using standard EPA exposure algorithms and generic unit exposure values from the PHED Version 1.1 (US EPA, 1998). The following exposure scenarios were assessed for agricultural workers:

Mixer/Loaders (M/L):
(1) M/L liquids for Aerial Application/ Chemigation;
(2) M/L liquids for Groundboom Applications;

Applicators:
(3) Applying by Enclosed Fixed Wing Aircraft;
(4) Applying by Groundboom [open cab];

Flagging
(5) Flagging in Support of Aerial Application;

Based on handler's activity use pattern, the duration of exposure is expected to be short-term (1 to 30 days) and intermediate term (1 to 6 months) for occupational handlers. Occupational workers may be exposed to fomesafen sodium during the mixing/loading and/or application process. Based on the product labels, fomesafen sodium can be applied at a maximum rate of 0.25 lbs ae/A on potatoes and 0.375 lbs ae/A on tomatoes. Maximum application rates have been assessed in this document to more inform risk managers about the specific conditions of the proposed label amendments. The adverse affects for short- and intermediate-term dermal risk assessment are female-specific; therefore the body weight of an average female (60 kg) was used to estimate dermal exposure. Since the adverse effects for the short- and intermediate-term inhalation endpoints are not gender specific, the body weight of an average adult (70 kg) was used to estimate inhalation exposure. Assumptions for the area treated per day were based on the EPA default values listed in ExpoSAC SOP #9.1. The work day was assumed to be 8 hours for all agricultural workers. For all use scenarios, the product application rates and amount handled per day are listed in Table 8.1.

Table 8.1. Application Rates Assessed and Quantity Handled per Day

Use Scenario	Crop Group	Application Rates Assessed (lb ae/A)	Area Treated per Day
Liquid: Aerial/ Chemigation Mixer/ Loader	Potato	0.25	350
	Tomato	0.375	
Liquid: Aerial Applicator	Potato	0.25	350
	Tomato	0.375	
Liquid: Groundboom Mixer/Loader; Applicator	Potato	0.25	80
	Tomato	0.375	
Flagging	Potato	0.25	350
	Tomato	0.375	

Risks were calculated as a MOE, which is a ratio of the toxicological Point of Departure (POD) to the daily dose. Daily dose values were calculated by first calculating exposures by considering application parameters (i.e., rate and area treated) along with unit exposures. Exposures were then normalized by body weight.

8.1.1 Occupational Handler Risk

The proposed label indicates that applications are made pre-emergence to potatoes and tomatoes. The proposed label allows for liquid application with a groundboom or an enclosed fixed wing aircraft. See Table 8.1.1 below.

For mixer/loaders at single layer dermal PPE (gloves, no respirator):

- For mixer/loader exposure scenarios, dermal and inhalation risks do not exceed HED's level of concern (i.e., the MOEs are greater than 100) at the proposed maximum application rate of 0.25 lbs ae /A for potatoes and 0.375 lb ae/A for tomatoes:
    - For mixer/loaders for aerial application/ chemigation on potatoes, the dermal MOE is 15,000 and the inhalation MOE is 330.
    - For mixer/loaders for aerial application/chemigation on tomatoes, the dermal MOE is 9,900 and the inhalation MOE is 220.
    - For mixer/loader for groundboom application on potatoes, the dermal MOE is 65,000 and the inhalation MOE is 1,500.
    - For mixer/loader for groundboom application on tomatoes, the dermal MOE is 43,000 and the inhalation MOE is 970.

For applicators at single layer dermal PPE (gloves, no respirator) for groundboom applicators or engineering control of enclosed cab for aerial applicators:

- For applicator scenarios, dermal and inhalation risks do not exceed HED's level of concern (i.e., the MOEs are greater than 100) at the maximum proposed application rate of 0.25 lbs ae /A for potatoes and 0.375 lb ae/A for tomatoes:
    - For applicators using engineering control of enclosed fixed wing aircraft application on potatoes, the dermal MOE is 62,000 and the inhalation MOE is 5,900.

- For applicators using engineering control of enclosed fixed wing aircraft application on tomatoes, the dermal MOE is 42,000 and the inhalation MOE is 3,900.
- For applicators using groundboom open cab on potatoes, the dermal MOE is 110,000 and the inhalation MOE is 2,400.
- For applicators using groundboom open cab on tomatoes, the dermal MOE is 71,000 and the inhalation MOE is 1,600.

For flagging at single layer dermal PPE (gloves, no respirator):

- For flagging scenarios, dermal and inhalation risks do not exceed HED's level of concern (i.e., the MOEs are greater than 100) at the maximum proposed application rate of 0.25 lbs ae /A for potatoes and 0.375 lb ae/A for tomatoes:
  - For flaggers open cab for tomatoes, the dermal MOE is 29,000 and the inhalation MOE is 1,100.
  - For flaggers open cab for tomatoes, the dermal MOE is 19,000 and the inhalation MOE is 760.

The proposed label requires single layer clothing and chemical-resistant gloves for all loaders, applicators, and other handlers. HED notes that the risk estimates on the proposed label PPE would have MOEs that do not exceed the LOC. Refer to Table 8.1.1 for detailed information.

Table 8.1.1. Short- and Intermediate-Term Fomesafen Sodium Occupational Handler Risk Estimates

Exposure Scenario	Crop	Application Rate[1] (lb ae/ acre)	Min PPE Dermal Unit Exposure[2] (mg/lb ae)	Baseline Inhalation Unit Exposure[3] (µg/lb ae)	Area Treated Daily[4] (acres)	Single Layer + Gloves Dermal Daily Dose (mg/kg/ day)[5]	Inhalation Daily Dose (mg/kg/ day)[6]	Single Layer + Gloves Dermal MOE[7]	Baseline Inhalation MOE[8]
Mixer/Loader Scenarios									
Mix/Load Liquids for Aerial Application / Chemigation	Potato	0.25	With Gloves: 0.023	1.2	350	0.0067	0.0015	15,000	330
	Tomato	0.375				0.01	0.00225	9,900	220
Mix/Load Liquids for Groundboom Application	Potato	0.25			80	0.0015	0.00034	65,000	1,500
	Tomato	0.375				0.0023	0.000514	43,000	970
Applicator Scenarios									
Applying Sprays by Enclosed Fixed-Wing Aircraft[9]	Potato	0.25	Eng. Control: 0.0055	Eng. Control: 0.068	350	0.0016	0.000085	62,000	5,900
	Tomato	0.375				0.0024	0.00013	42,000	3,900
Applying Sprays by Open Cab Groundboom	Potato	0.25	With Gloves: 0.014	0.74	80	0.00093	0.00021	110,000	2,400
	Tomato	0.375				0.0014	0.00032	71,000	1,600
Flagger Scenario									
Flagging for Liquid Aerial Application	Potato	0.25	With Gloves: 0.012	0.35	350	0.0035	0.00044	29,000	1,100
	Tomato	0.375				0.00525	0.00066	19,000	760

[1]Application rates are based on maximum values found on the label.

[2]Minimum PPE dermal unit exposure represent long pants, long sleeved shirts, shoes, socks and chemical-resistant gloves. Engineering control unit exposures represent use of enclosed cab. Values are reported in the PHED Surrogate Exposure Guide dated August 1998.
[3] Baseline Inhalation unit exposures represent no respirator protection (baseline). Engineering control unit exposures represent use of enclosed cab. Values are reported in the PHED Surrogate Exposure Guide dated August 1998.
[4]Area treated daily values are from the EPA HED estimates of acreage treated in a single day for each exposure scenario of concern.
[5]Daily Dermal Dose = (Dermal Unit Exposure (mg ae /lb ae) * Application Rate (lb ai /A) * Area Treated (A /day)) / Body Weight (60 kg) * 20% Dermal Absorption (0.20)
[6] Daily Inhalation Dose = (Inhalation Unit Exposure (µg ae /lb ae) * Conversion Factor (1 mg /1000 µg) * Application Rate (lb ae/A) * Area Treated (A/day))/ Body Weight (70 kg)
[7] Dermal MOE = PoD (NOAEL of 100 mg/kg/day)/ Daily dermal dose (mg/kg/day)
[8] *Inhalation MOE = PoD (NOAEL of 0.5 mg/kg/day) / Daily inhalation dose (mg/kg/day)*
[9] Application by fixed-wing aircraft has engineering control of enclosed cab.

8.2 Occupational Post-application Exposure

As the proposed label states that the product is applied to potatoes as a broadcast pre-emergence application after planting but before potato emergence, post-application exposures are not anticipated for this use. Also, as the product is applied as a pre-plant non-incorporated pre-emergence broadcast application prior to transplanting tomatoes; post-application exposures are not anticipated for this use; therefore a quantitative post-application exposure assessment was not conducted.

This risk assessment for fomesafen sodium evaluates the potential risks associated with its pre-plant/pre-emergent uses on tomatoes and potatoes. There is a low potential for occupational post-application exposure associated with the use of pre-plant/pre-emergent herbicides because there are no hand labor activities typically associated with the production of crops that would require significant contact with treated soil and no foliage is present that could also lead to exposure via contact including potatoes and tomatoes. There is a possible concern that some level of soil contact could occur during mechanically assisted tomato transplanting activities, however, but this is likely to result in negligible exposures as outlined in HED Exposure SAC Policy 8. This is because transplanting activities involve moving starter plants onto a rotating wheel while riding upon an implement being moved across a field. In such cases there would be minimal contact with machinery that has small amounts of field soil on it because of the possibility of mechanical injury. Also, commercial tomato cultivation is typically in tarped, raised beds with small planting holes punched in the tops of the raised beds which also minimizes the potential for contact with treated soil because of the physical barrier. These conclusions are appropriate even though fomesafen sodium has a long half-life in soil (i.e., mean soil half life of ~390 days).

9.0 Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.epa.gov/compliance/resources/policies/ej/exec_order_12898.pdf. The Office of Pesticide Programs (OPP) typically considers the highest potential exposures from the legal use of a pesticide when conducting human health risk assessments, including, but not limited to, people who obtain drinking water from sources near agricultural areas, the variability of diets

within the U.S., and people who may be exposed when harvesting crops. Should these high exposures indicate potential risks of concern, OPP further refines the risk assessments to ensure that the risk estimates are based on the best available information.

10. 0 Data Needs

Toxicology

The following toxicology data gaps exist:

869.1200 Acute Dermal Toxicity Study
870.1300 Acute Inhalation Toxicity Study
869.2600 Skin Sensitization Study
870.7200 Acute Neurotoxicity Study
870.7200 Subchronic Neurotoxicity Study
870.7800 Immunotoxicity Study

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 **tomatoes**.

860.1200 Directions for Use

- At this time, data are not available to support rotation to other crops beyond those commodities that are currently registered and proposed as primary crops; therefore, the petitioner must revise the Reflex® Herbicide label to permit immediate replanting of soybeans, cotton, dry beans, snap beans, and tomatoes 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.

860.1850 Confined Accumulation in Crops

- The ongoing confined rotational crop study, which was expected to be completed by 12/2009, should be submitted. Based on this future submission, HED will determine the terminal residues of concern in rotational crops and will re-evaluate the existing field rotational crop studies for determination of appropriate plantback restrictions.

HED cannot recommend for the requested tolerance in/on potatoes due to the lack of an adequate root/tuber metabolism study. The following study must be submitted to support the proposed tolerance.

860.1300 Plant Metabolism

- A potato metabolism study in which both the roots and tops are analyzed is required to support the proposed use and tolerance on potatoes.

Occupational and Residential Exposure

None.

11.0 References

Occupational/Residential Exposure:

Fomesafen Sodium: Occupational Exposure Assessment for a Proposal to Add New Uses on Potatoes and Tomatoes, D373961, A. LaMay, 2/19/2010.

Dietary:

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Water:

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

Drinking Water Assessment for Fomesafen use on cotton, soybeans, dry beans, snap beans, potato and tomato, D365204, J. Lin, 12/10/2009.

Endpoint Selection:

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

Fomesafen Sodium: Response to a request by Syngenta Crop Protection, Inc. for revision of the toxicity endpoints and unit exposures for the occupational exposure assessment, D337945, W. Phang and M. Lloyd, 4/29/08.

Appendix A: Toxicology Assessment

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.500) 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	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	no
870.1300	Acute Inhalation Toxicity	yes	no
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	no
870.3100	Oral Subchronic (rodent)	yes	yes
870.3150	Oral Subchronic (nonrodent)	yes	yes
870.3200	21-Day Dermal	yes	yes
870.3250	90-Day Dermal	no	-
870.3465	90-Day Inhalation	no	-
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	no
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	yes	yes
870.4100b	Chronic Toxicity (nonrodent)	yes	yes
870.4200a	Oncogenicity (rat)	yes	yes
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation – mammalian	yes	yes
870.5xxx	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a	Acute Delayed Neurotox. (hen)	no	-
870.6100b	90-Day Neurotoxicity (hen)	no	-
870.6200a	Acute Neurotox. Screening Battery (rat)	yes	**no**
870.6200b	90-Day Neuro. Screening Battery (rat)	yes	**no**
870.6300	Develop. Neuro	no	-
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	yes	no
870.7800	Immunotoxicity	yes	**no**

A.2 Toxicity Profiles

Table A.2.1 Acute Toxicity Profile- Fomesafen

Guideline	Study Type (Date)	MRID	Results	Tox. Cat.
870.1100 (§ 81-1)	Acute Oral	00247589	LD_{50} = 1250-2000 mg/kg	III
870.1200 (§ 81-2)	Acute Dermal	-	-	-
870.1300 (§ 81-3)	Acute Inhalation	-	-	-
870.2400 (§ 81-4)	Primary Eye Irritation	00247589	Severe Irriation	-
870.2500 (§ 81-5)	Primary Dermal Irritation	00247589	Moderate Irriation	-
870.2600 (§ 81-6)	Dermal Sensitization	-	-	-

Table A.2.2 Subchronic, Chronic, and Other Toxicity Profile

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 transminase in males
870.3150 26-Week dogs- diet	0.00103014 (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)

Guideline No./Study Type	MRID No. (year)/ Classification/Doses	Results
870.3200 21-day dermal-rabbit	00135632 (1983) Acceptable/ Guideline 0, 10, 100 or 1000 mg/kg/day	NOAEL = 1000 mg/kg/day LOAEL was not observed
870.3700 Prenatal development toxicity- rabbit	00109214 (1981) Unacceptable/Guideline 0, 2.5, 10 or 40 mg/kg/day	At 40 mg/kg/day, does appeared thin and had increased incidence of stomach erosions. No significant difference between controls and treated animals for developmental abnormalities. Study provided information to assess potential developmental toxicity rabbits, but was classified unacceptable because of bacterial infection in the colony.
870.3700 Prenatal development 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 (DP316263, 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 the staining of the ventral fur and significantly decreased body weight gain (>10%) Developmental NOAEL = 100 mg/kg/day Developmental LOAEL = 200 mg/kg/day based on postimplantation loss observed in study CTL/P/576 (MRID 00164903)
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 fomesagen.] Maternal NOAEL = 100 mg/kg/day Maternal LOAEL = 200 mg/kg/day based on the staining of the ventral fur and significantly decreased body weight gain (>10%) Developmental NOAEL = 100 mg/kg/day Developmental LOAEL = 200 mg/kg/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)	Paternal NOAEL = 250 ppm (12.5 mg/kg/day) Paternal 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

Guideline No./Study Type	MRID No. (year)/ Classification/Doses	Results
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

Appendix B. Toxicity Summaries

MRID No. 00103013

Citation 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.

MRID No. 00103014

Citation 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).

MRID No. 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 No. 00103016

Citation 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).

MRID No. 00109214

Citation 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.

MRID No. 00131491

Citation 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).

MRID No. 00135632

Citation 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.

MRID No. 00142125

Citation 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.

MIRD No. 00144862

Citation 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 F1A pups were weaned on postnatal day (PND)22 and F1B, F2B and F2A pups were weaned PND 29. Thirty F1B females and 15 males were selected to

become F1 parents and produced F2B 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, increased incidences of liver alterations were seen male and female F0 and F1 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 F1b males, however, these effects are considered to be of systemic effect rather than offspring toxicity. No liver alterations 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 F1b 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 F1and F2 A litter at 250 ppm. A significant reduction 20% in litter size was observed at 1000 ppm F2B 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 F1 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.

MRID No. 00164903

Citation 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).

MRID No. 40786709

Citation 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 ~50 ppm and in females at ~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.

MRID No. 44569805

Citation 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.

MRID No. 44569806

Citation 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 C: Review of Human Research

In the PHED study, adult human subjects were intentionally exposed to a pesticide and it has been determined that a review of their ethical conduct is required.

- The PHED Task Force, 1995. The Pesticide Handler Exposure Database (PHED), Version 1.1. Task Force members Health Canada, U.S. Environmental Protection Agency, and the National Agricultural Chemicals Association, released February 1995.

The PHED study has received the appropriate ethical review.

Appendix D: Rationale for Toxicology Data Requirements

Guideline Number: 870.7800 **Study Title: Immunotoxicity**
Rationale for Requiring the Data
The immunotoxicity study is a new data requirement under 40 CFR Part 158 as a part of the data requirements for registration of a pesticide (food and non-food uses). The Immunotoxicity Test Guideline (OPPTS 870.7800) prescribes functional immunotoxicity testing and is designed to evaluate the potential of a repeated chemical exposure to produce adverse effects (i.e., suppression) on the immune system. Immunosuppression is a deficit in the ability of the immune system to respond to a challenge of bacterial or viral infections such as *tuberculosis* (TB), Severe Acquired Respiratory Syndrome (SARS), or neoplasia. Because the immune system is highly complex, studies not specifically conducted to assess immunotoxic endpoints are inadequate to characterize a pesticide's potential immunotoxicity. While data from hematology, lymphoid organ weights, and histopathology in routine chronic or subchronic toxicity studies may offer useful information on potential immunotoxic effects, these endpoints alone are insufficient to predict immunotoxicity.
Practical Utility of the Data
How will the data be used? Immunotoxicity studies provide critical scientific information needed to characterize potential hazard to the human population on the immune system from pesticide exposure. Since epidemiologic data on the effects of chemical exposures on immune parameters are limited and are inadequate to characterize a pesticide's potential immunotoxicity in humans, animal studies are used as the most sensitive endpoint for risk assessment. These animal studies can be used to select endpoints and doses for use in risk assessment of all exposure scenarios and are considered a primary data source for reliable reference dose calculation. For example, animal studies have demonstrated that immunotoxicity in rodents is one of the more sensitive manifestations of TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) among developmental, reproductive, and endocrinologic toxicities. Additionally, the EPA has established an oral reference dose (RfD) for tributyltin oxide (TBTO) based on observed immunotoxicity in animal studies (IRIS, 1997). **How could the data impact the Agency's future decision-making?** If the immunotoxicity study shows that the test material poses either a greater or a diminished risk than that given in the interim decision's conclusion, the risk assessments for the test material may need to be revised to reflect the magnitude of potential risk derived from the new data.

Guideline Number: 870.7200 **Study Title: Acute and Subchronic Neurotoxicity**
Rationale for Requiring the Data
Acute and subchronic neurotoxicity studies are now required under 40 CFR Part 158 as a part of the data requirements for registration of a pesticide for (food and non-food uses). The Neurotoxicity Test Guideline (OPPTS 870.6200) require a functional observational battery, motor activity, and neuropathology evaluation. The functional observational battery consists of noninvasive procedures designed to detect gross functional deficits in animals and to better quantify behavioral or neurological effects detected in other studies. The motor activity test uses an automated device that measures the level of activity of an individual animal. The neuropathological techniques are designed to provide data to detect and characterize

histopathological changes in the central and peripheral nervous system. This battery is designed to be used in conjunction with general toxicity studies and changes should be evaluated in the context of both the concordance between functional neurological and neuropatholgical effects, and with respect to any other toxicological effects seen.
Practical Utility of the Data
How will the data be used? Neurotoxicity studies provide critical scientific information needed to characterize potential hazard to the human population of neurotoxicity from pesticide exposure. **How could the data impact the Agency's future decision-making?** If the neurotoxicity study shows that the test material poses either a greater or a diminished risk than that given in the risk assessments's conclusion, the risk assessments for the test material may need to be revised to reflect the magnitude of potential risk derived from the new data.

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R180904

Chemical Name: Sodium salt of fomesafen

PC Code: 123802
HED File Code: 14000 Risk Reviews
Memo Date: 2/19/2010
File ID: 00000000
Accession #: 000-00-0134

HED Records Reference Center
2/24/2010