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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: February 12, 2002

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

MEMORANDUM

Subject: **Triflusulfuron-methyl**: Human Health Risk Assessment for the Section 3 Registration on Sugar Beets (PP#4F4278) and Chicory (PP#0E6214)

DP Barcode:	D260076	Case:	285206, 293405
PC Code:	129002	Class:	Herbicide
Trade Name:	UpBeet	EPA Reg. No.:	352-569
40 CFR	180.492		

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1.0 Executive Summary

HED issued a human health risk assessment for triflusulfuron-methyl in 1996 (S. Robbins, 6/18/96, DP Barcode D210095). Due to data gaps, the Agency established time-limited tolerances for residues of this herbicide in/on sugar beet roots and tops (both at 0.05 ppm; PP#4F4278). Since then, the data gaps have been resolved. Because the previous risk assessment was conducted prior to the enactment of the Food Quality Protection Act, this FQPA-compliant risk assessment is required in order to establish permanent tolerances for residues of triflusulfuron-methyl in/on sugar beet commodities. This risk assessment also addresses the recently requested use of triflusulfuron-methyl on chicory (PP#0E6214).

Triflusulfuron-methyl is a sulfonylurea herbicide that inhibits the biosynthesis of branched-chain amino acids in plants (via inhibition of the plant enzyme acetolactate synthase). Marketed as UpBeet, a dry-flowable formulation containing 50% ai, triflusulfuron-methyl may be broadcast (ground- or aerial-based) or band applied at seasonal rates of up to 0.078 lb ai/A. Toxicological effects in mammals noted for triflusulfuron-methyl were decreased body weight and body weight gain, alterations in hematology (particularly in males), and increased interstitial cell hyperplasia in testes. No toxicological effects were attributable to a single, oral (i.e., acute) exposure. In dermal exposure studies, no effects were observed at the highest dose tested. For assessment of inhalation exposures, route-to-route extrapolation from oral exposures has been used, assuming 100% absorption for inhalation exposures. Triflusulfuron-methyl has been classified as a Category C "possible human carcinogen" and the PAD-based chronic risk assessment is sufficiently protective of human health. The FQPA Safety Factor to account for enhanced sensitivity of infants and children has been removed (i.e., reduced to 1×) because there is no evidence of increased susceptibility in rat or rabbit fetuses from the developmental toxicity studies, the effects in the offspring observed during the 2-generation reproductive toxicity study can be attributed to the decreases in body weights seen in the parental animals, and no neuropathological or neurobehavioral effects in the acute or subchronic neurotoxicity studies were observed.

At present, there are no non-agricultural use sites for triflusulfuron-methyl; thus, for non-occupational exposure, the only pathway of exposure is via the diet (sugar beet commodities, chicory, and drinking water). In assessing the human health risks associated with the requested uses of triflusulfuron-methyl, HED has examined occupational exposure to workers involved in mixing/loading/ application activities as well as post-application activities, and has considered aggregate dietary exposure from food and drinking water sources. All occupational margin of exposure estimates are greater than 100 and, therefore, represent risks that are below HED's level of concern. Since the hazard associated with dermal exposure is negligible, risks associated with postapplication activities are not of concern. To assess aggregate dietary exposure, the Agency does not have adequate water residue data (e.g., drinking water monitoring data) with which to quantitatively estimate the aggregate dietary exposure. In the absence of such data, HED has calculated Drinking Water Levels of Comparison (DWLOCs) as a metric for comparison to model-derived Estimated Environmental Concentrations (EECs). The DWLOCs for chronic dietary exposures for all population subgroups are at least three orders of magnitude greater than

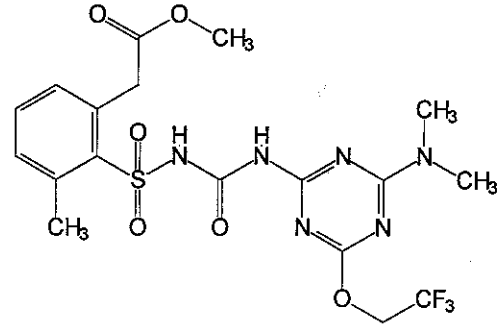
the EECs, indicating that aggregate exposure to triflusulfuron-methyl will be less than HED's level of concern.

The aggregate human health risk estimates associated with the use of triflusulfuron-methyl on sugar beets and chicory are below HED's level of concern for all scenarios and population subgroups, including those of infants and children, and the previous data gaps associated with the sugar beet use have been resolved. Therefore, HED recommends that the time-limited tolerances for residues of triflusulfuron-methyl in/on beet, sugar, root and beet, sugar, top (each at 0.050 ppm) be converted to permanent tolerances and that a tolerance be established for residues of triflusulfuron-methyl in/on chicory at 0.050 ppm. The registration should be made conditional pending the receipt of a 28-day inhalation (nose only) toxicity study.

HED notes that the petitioner has listed a 4-hour REI on the UpBeet label. Acute toxicity information is available for the technical which indicates that all six acute toxicity tests have been classified as Category III or IV (Table 2). Based on toxicity information on the active ingredient Triflusulfuron-methyl, it is a candidate for a 4-hour REI. However, in order for a 4-hour REI to be accepted by the EPA, the registrant must submit toxicity information on the end-use product and must provide a certification to the Agency regarding postapplication incidents. PR Notice 95-3 provides details on the process of applying for a 4-hour REI. Alternatively, the petitioner may revise the label to specify a 12-hour REI.

2.0 Characterization of Physicochemical Properties

Triflusulfuron-methyl is a sulfonylurea herbicide with a molecular weight of 492 Daltons and a melting point of 155 - 158°C. The water solubility of triflusulfuron-methyl is highly pH dependent. At pH 5, the solubility is 2.7 ppm, whereas at pH 9 the solubility increases to 11000 ppm. This herbicide has a vapor pressure of less than 1×10^{-7} mm Hg. Exposure to triflusulfuron-methyl via volatilization is extremely unlikely.



Triflusulfuron-methyl is a non-persistent compound. While its low adsorption coefficients and high water solubility at environmental pHs indicate that triflusulfuron-methyl may leach to groundwater, its short half-life suggests that it will not accumulate from repeated applications in either surface or ground water.

3.0 HAZARD CHARACTERIZATION

Triflusulfuron-methyl has low toxicity by the acute oral, acute inhalation and primary dermal routes. In the acute dermal and primary eye irritation studies, minimal toxicity is seen. In addition, there is no evidence of dermal sensitization.

Subchronic studies with triflusulfuron-methyl resulted in no evidence of dermal or systemic toxicity in rabbits at the limit dose. In a 90-day oral toxicity study in rats, evidence of decreased mean body weight and mean body weight gain, decreased mean food consumption (females), decreased mean food efficiency, altered hematology parameters (males) and hemosiderin deposition in the kidneys (females) was observed. In a second 90-day oral study in rats, decreased body weight gain and food efficiency in males and increased incidence of histopathological changes in females was observed. In a 13-week subchronic oral toxicity study in beagle dogs, decreased group mean body weight and body weight gain, decreased erythrocytes, hemoglobin and hematocrit; increased SGOT, SGPT, and alkaline phosphatase; increased absolute and relative liver weight; and decreased testes weight. Microscopic abnormalities of the testes and liver were observed.

Long-term dietary administration of triflusulfuron methyl in beagle dogs resulted in increases in alkaline phosphatase (males), liver weight, and minimal centrilobular hypertrophy. There was no evidence of tumors. In a combined chronic toxicity/carcinogenicity study in rats, chronic toxicity is based on decreased body weight and body weight gain, alterations in the hematology parameters (males predominately) and an increased incidence of interstitial cell hyperplasia of the testicles in males. It is carcinogenic in male CD rats, inducing interstitial cell tumors (adenomas) in the testes. In a carcinogenicity study in mice, toxicity is based on increases in liver weights and increased incidence of microscopic changes in the liver (increased incidence of hepatic tumors in male mice).

Triflusulfuron-methyl is classified as a Group C - possible human carcinogen- chemical and for the purpose of risk characterization the RfD approach should be used for quantification of human risk. This is based on evidence of highly significant, dose-related increases in the incidence of interstitial cell adenomas in the rat at two doses. Evidence of a hormonal basis for these tumors is suggestive, but not conclusive. The mutagenicity studies provide wome evidence of clastogenic activity. The evidence from structurally related analogs was mixed; of twelve chemicals in this class (sulfuronyl ureas), primisulfuron methyl, prosulfuron, and tribenuron methyl (Express) have been associated with carcinogenic activity in rodents.

Results were negative for mutagenicity in two Ames assays, a CHO gene mutation assay, as well as a mouse micronucleus assay. Three metabolites were also non-mutagenic in Ames assays. In structural chromosomal aberration testing using human lymphocytes, the results were positive (in the presence of metabolic activation) and inconclusive (in the absence of metabolic activation) for both parent triflusulfuron methyl as well as the metabolites.

There is no quantitative or qualitative evidence of increased susceptibility of rat or rabbit fetuses to *in utero* exposure in developmental toxicity studies. The developmental NOAELs are either higher than or equal to the maternal NOAELs. There were no developmental findings in rats up to the limit dose of 1000 mg/kg/day. In rabbits, abortions were seen in the presence of maternal toxicity (death, decreased body weight and food efficiency as well as clinical signs).

In a 2-generation reproductive toxicity study, the effects in the offspring (decreased pup body weight in F1) were not considered to be indicative of severity because the decreases were seen on Days 14 and 21 (late lactation). During this period, the pups were exposed to the test material by both the milk and diet, when the young rats consume approximately twice the diet per unit body weight as an adult rat consumes. In addition, this decrease was seen only in the F1 generation but not in the second generation.

There is no indication for the need of a developmental neurotoxicity studies because no neuropathological or neurobehavioral effects were seen in either the acute or subchronic neurotoxicity study as well as in other studies in the data base. There are no alterations of fetal development of the nervous system, lesions in adults are mild and late occurring, and there are no SAR concerns.

In a metabolism study, the liver, (as well as the ovaries and skin at the high dose), had a significant proportion of residual radioactivity at 120 hours post-dose at all dose levels. Urine was the major route of excretion at the low dose, with feces being the major route at the high dose. The major urinary metabolite (N-desmethyl triflusulfuron-methyl) composed between 25-44% of the dose at the low dose. Females rats showed higher urinary levels than males of this metabolite. The N-hydroxymethyl metabolite was also found in urine, but did not vary significantly with dose. The triazine metabolites of triflusulfuron-methyl (Triazine amine, N-desmethyl triazine amine, N,N-bis-desmethyl triazine amine) were found in urine and liver. The parent chemical was found as a major component only in feces and liver from high dose treatments.

3.1 Hazard Profile

Table 1. Acute Toxicity for Triflusulfuron-methyl Technical Material

Guideline No.	Test	Result	Tox Category
81-1 870.1100	Acute Oral (Rat)[1]	LD_{50} (M & F)[2] > 5000 mg/kg	IV
81-2 870.1200	Acute Dermal (Rat)[1]	LD_{50} (M & F) > 2000 mg/kg	III
81-2 870.1200	Acute Dermal (Rabbit)[3]	LD_{50} (M & F) > 2000 mg/kg	III
81-3 870.1300	Acute Inhalation (Rat)[4]	LC_{50} (M & F) > 5.1 mg/L	IV
81-4 870.2400	Primary Eye Irritation (Rabbit)[5]	Slight irritation of conjunctiva and cornea which cleared within 72 hrs.	III
81-5 870.2500	Primary Dermal Irritation (Rabbit)[5]	Slight irritation clearing within 48 hrs.	IV
81-6 870.2600	Dermal Sensitization (Guinea pig)[1]	No evidence of dermal sensitization	n/a
81-7 870.6100	Acute Neurotoxicity	NOAEL $\geq$ 2000 mg/kg (limit dose)	-

[1] Test material = 98% a.i.
[2] M = Male and F = Female
[3] Test material = 95.6% a.i.
[4] Test material = 94.9% a.i.
[5] Test material = 96.7% a.i.

Table 2. Toxicity Profile of Triflusulfuron-methyl Technical Material	
Guideline No./ Study Type	Results
870.3100 90-Day oral toxicity in rats	NOAEL = 6.56/7.71 mg/kg/day in m/f LOAEL = 133/153 mg/kg/day in m/f, based on decreased body weight gain and food efficiency in males; increased incidence of histopathological changes (kidney & spleen) in females
870.3100 90-Day oral toxicity in rats	NOAEL = 6.20/7.54 mg/kg/day in m/f LOAEL = 127/150 mg/kg/day in m/f, based on decreased mean body weight and body weight gain, decreased mean food consumption (f), decreased mean food efficiency, alterations in hematology parameters (m); hemosiderin in kidneys (f)
870.3150 90-Day oral toxicity in dogs	NOAEL = 3.9/3.7 mg/kg/day in m/f LOAEL = 146.9/159.9 mg/kg/day based on decreased mean body weight and body weight gain, decreased hematocrit, hemoglobin, RBC's, SGOT, SGPT, ALP, absolute and relative liver and testes weight; microscopic abnormalities of the liver and testes.
870.3200 21-Day dermal toxicity in rabbits	NOAEL $\geq$ 1000 mg/kg/day (Limit dose) LOAEL > 1000 mg/kg/day (Limit dose)
870.3700 Prenatal developmental toxicity in rats	**Maternal** NOAEL = 120 mg/kg/day LOAEL = 350 mg/kg/day based on decreased body weight gain, decreased food consumption and lower food efficiency. **Developmental** NOAEL = $\geq$ 1000 mg/kg/day (Limit dose) LOAEL = > 1000 mg/kg/day.
870.3700 Prenatal developmental toxicity in rabbits	**Maternal** NOAEL = 90 mg/kg/day LOAEL = 270 mg/kg/day based on clinical signs including absent/reduced stool and stained fur, maternal death, increased abortions, decreased body wt gain, and lower food efficiency. **Developmental** NOAEL = 90 mg/kg/day LOAEL = 270 mg/kg/day based on increased abortions.
870.3800 Reproduction and fertility effects	**Parental/Systemic** NOAEL = 5.81/7.75 mg/kg/day in m/f LOAEL = 44/58 mg/kg/day in m/f based on decreased body wt., decreas. body wt. gain, decreased food consumpt., and decreased food efficiency. **Reproductive** NOAEL = $\geq$ 89.5/115 mg/kg/day in m/f based on the absence of repro effects at the HDT. LOAEL = > 115 mg/kg/day. **Offspring** NOAEL = 5.81/7.75 mg/kg/day in m/f LOAEL = 44/58 mg/kg/day in m/f based on decreased F1 pup body wt. on days 14 & 21 due to exposure via milk and in the diet.

Guideline No./ Study Type	Results
870.4100a Chronic toxicity rats	NOAEL = 2.44 mg/kg/day LOAEL = 30.6 mg/kg/day based on decreased body weight and body weight gain, alter. in hematology (mainly males) and increased incidences of interstitial cell hyperplasia in testes.
870.4100b Chronic toxicity dogs	NOAEL = 26.9 mg/kg/day LOAEL = 111.6 mg/kg/day based on increased liver weight, alkaline phosphatase, and hepatocellular hypertrophy.
870.4200 Carcinogenicity rats	NOAEL = 2.44 mg/kg/day LOAEL = 30.6 mg/kg/day based on decreased body weight and body weight gain, alter. in hematology (mainly males) and increased incidences of interstitial cell hyperplasia in the testes.
870.4300 Carcinogenicity mice	NOAEL = 14.6 mg/kg/day LOAEL = 349 mg/kg/day based on increased liver wt. and increased hepatic cell tumors (adenomas and/or carcinomas combined). Possible evidence of carcinogenicity
870.5000 Gene Mutation	No genotoxic effect in Ames assay using S. typhimurium. (2 studies)
870.5300 Cytogenetics	No genotoxic effect in CHO gene mutation assay.
870.5300 Other Effects	Positive effects in the presence of metabolic activation, but inconclusive in the absence of metabolic activation in a chromosomal aberration/human lymphocyte study.
870.5300 Other Effects	Mouse micronucleus assay is negative for genotoxic effects.
870.6200a Acute neurotoxicity screening battery	NOAEL = $\geq$ 2000 mg/kg/day (HDT) LOAEL = not established
870.6200b Subchronic neurotoxicity screening battery	Systemic NOAEL = 92.7/7.1 mg/kg/day in m/f. Systemic LOAEL = 186.2/51.6 mg/kg/day in m/f, based on decreased body weight and body weight gain.
870.7485 Metabolism and pharmacokinetics	Urine major route of excretion at low doses and the feces at high doses. N-desmethyl triflusulfuron methyl, the major urinary metabolite composed between 25-44% of the dose at the low dose level (single and repeated). Parent was the major component in high dose feces and liver.
870.7600 Dermal penetration	No dermal absorption studies were available. A 27% absorption was calculated from a ratio of the LOAEL from a developmental and 21-day dermal toxicity studies in rabbits.
Special studies: *In vivo* and *in vitro* mechanistic studies.	The purpose of these studies was to investigate the mechanism of Leydig cell tumor induction in the testes of male rats. A dose-dependent decrease in aromatase enzyme activity was seen *in vitro*, but was inconclusive *in vivo*.

3.2 FQPA Considerations

There is no quantitative or qualitative evidence of increased susceptibility of rat or rabbit fetuses to *in utero* exposure in the developmental studies. No developmental toxicity was seen at

the limit dose (1000 mg/kg/day) in rats. In rabbits, developmental toxicity manifested as abortions in the presence of severe maternal toxicity (mortality, abortions, clinical signs, decreased body weight and food efficiency). In the 2-generation reproductive toxicity study, the effects in the offspring (decreased pup body weight in F1 on Days 14 and 21; late lactation) can be attributed to the decreases in body weights seen in the parental animals. In addition, this decrease was seen only in the F1 generation but not in the second generation.

There is no indication for a developmental neurotoxicity study since no neuropathological or neurobehavioral effects in the acute or subchronic neurotoxicity studies were observed; no alteration of the fetal nervous system was observed; and no evidence of neurotoxicity was found in other studies in the database.

3.3 Dose-Response Assessment

Acute RfD: An acute RfD (aRfD) can not be established since there are no toxicological effects attributable to a single exposure (dose) observed in any of the oral toxicity studies. Therefore this risk assessment is not required.

Chronic RfD: The chronic reference dose (cRfD) of 0.024 mg/kg/day was determined where the NOAEL of 2.44 mg/kg/day is based on decreased body weight gain, alterations in hematology (mainly in males), and increases in the incidence of interstitial hyperplasia in the testes at the LOAEL of 30.6 mg/kg/day. A 100-fold uncertainty factor (UF) for interspecies extrapolation and intraspecies variability was applied. Therefore, the cRfD is 0.024 mg/kg/day.

Carcinogenicity: In accordance with the criteria contained in the EPA's "Guidelines for Carcinogen Risk Assessment" [FR51: 33992-34003, 1986] for classifying the weight of evidence for carcinogenicity, HED's Carcinogenicity Peer Review Committee (CPRC) determined that triflusulfuron methyl should be classified as a Group C chemical and that for the purpose of risk characterization the RfD approach should be used for quantification of human risk. This was based on evidence of highly significant, dose-related increases in the incidence of interstitial cell adenomas in the rat testes at two doses. Evidence of a hormonal basis for these tumors was suggestive, but not conclusive. The evidence from structurally related analogs was mixed; of twelve chemicals in this class (sulfuronyl ureas), primisulfuron-methyl, prosulfuron and tribenuron-methyl (Express) have been associated with carcinogenic activity in rodents.

Mutagenicity: Triflusulfuron-methyl was negative for mutagenicity in two Ames assays, a CHO gene mutation assay as well as a mouse micronucleus assay. Three metabolites were also non-mutagenic in Ames assays. In structural chromosomal aberration testing using human lymphocytes, the results were positive (in the presence of metabolic activation) and inconclusive (in the absence of metabolic activation) for both parent triflusulfuron-methyl as well as the metabolites.

Incidental oral exposure: For short- and intermediate-term incidental oral exposure, the NOAEL of 7.1 mg/kg/day from a subchronic rat study was selected as the endpoint. This was based on decreased body weight gain and is appropriate for the population subgroup (infants and

children) of concern for both short-term as well as intermediate-term duration (since the decrease was seen between days 1 through 8, and was sustained through week 13).

Dermal Penetration: There were no dermal absorption studies available. As an alternative to assuming 100% dermal absorption by default, and because the molecular weight of triflusulfuron-methyl is large and it is a solid, a conservative estimate was extrapolated. An upper bound estimation of 27% was calculated from the ratio of the LOAEL of 270 mg/kg/day established in the developmental toxicity study in rabbits to the NOAEL of 1000 mg/kg (assumed to be a LOAEL on a worst case scenario) in the 21-day dermal toxicity study in rabbits.

Dermal toxicity: For short- and intermediate-term dermal exposure, no systemic toxicity was seen in rabbits at the limit dose following dermal applications for 21 days. No hazard was identified, therefore, quantification of dermal risk is not required.

For long-term dermal exposure, an oral dose endpoint at the NOAEL of 2.44 mg/kg/day was selected. Since an oral dose was chosen, a 27% dermal absorption factor should be used for route-to-route extrapolation.

Inhalation toxicity: For short- and intermediate-term inhalation exposure, an oral dose endpoint was selected based on a subchronic toxicity study in rats. The HIARC determined that since oral endpoints were selected for these exposures, a 100% inhalation absorption factor should be used for route-to-route extrapolation.

For long-term inhalation exposure, an oral dose endpoint based on a chronic feeding study in rats was selected. The HIARC determined that since oral endpoints were selected for these exposures, a 100% inhalation absorption factor should be used for route-to-route extrapolation.

Table 3. Triflusulfuron-methyl: Summary of Toxicological Doses and Endpoints for Use in Human Health Risk Assessments

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF* and Endpoint for Risk Assessment	Study and Toxicological Effects
Acute Dietary <u>all population subgroups</u>	N/A	No toxicological effects attributable to a single exposure (dose) were observed in oral toxicity studies. Therefore, an acute RfD can not be established and an acute dietary risk assessment will not be required for the general population.	
Chronic Dietary <u>all populations</u>	NOAEL= 2.44 mg/kg/day UF = 100 Chronic RfD = 0.024 mg/kg/day	FQPA SF = 1x **cPAD** = <u>chronic RfD</u> FQPA SF =0.024 mg/kg/day	Chronic Toxicity in Rats LOAEL of 30.6 mg/kg/day based on decreased body weight and body weight gain, alter. in hematology (mainly males), increased incidence of interstitial cell hyperplasia in testes.

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF* and Endpoint for Risk Assessment	Study and Toxicological Effects
Short-term Incidental Oral	NOAEL = 7.1 mg/kg/day Target MOE = 100	Decreased body weight gain seen during days 1-8 at 153 mg/kg/day (LOAEL)	90-Day Rat
Intermediate-term Incidental oral	NOAEL= 7.1 Target MOE = 100	Decreased mean body weight seen throughout the study	90-day Rat
Short- and Intermed.-Term Dermal (Residential)	No systemic toxicity was seen at the Limit Dose following repeated dermal applications. No developmental toxicity concern was identified. Therefore, no hazard was identified and quantification of dermal risk assessment is not required.		
Long-Term Dermal	NOAEL = 2.44 Target MOE = 100	Decreased body weight and body weight gain, alterations in hematology (mainly males), increased incidence of interstitial cell hyperplasia in testes.	Rat Chronic feeding
Short-term Inhalation	NOAEL= 7.1 100% inhalation absorption factor Target MOE = 100	Decreased body weight gain seen during days 1-8 at 153 mg/kg/day (LOAEL)	90-Day Rat
Intermediate-term Inhalation	NOAEL= 7.1 100% inhalation absorption factor Target MOE = 100	Decreased mean body weight seen throughout the study	90-day Rat
Long-Term Inhalation	NOAEL = 2.44 100% inhalation absorption factor Target MOE = 100	Decreased body weight and body weight gain, alterations in hematology (mainly males), increased incidence of interstitial cell hyperplasia in testes.	Rat Chronic feeding
Cancer (oral, dermal, inhalation)	Triflusulfuron-methyl is classified as a Group C - possible human carcinogen- chemical.		

* The reference to the FQPA Safety Factor refers to any additional safety factor retained due to concerns unique to the FQPA.

3.4 Endocrine Disruption

EPA is required under the Federal Food Drug and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all

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

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, triflusulfuron-methyl may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 Exposure Assessment

4.1 Summary of Registered Uses

Triflusulfuron-methyl is a herbicide of the sulfonylurea class intended to control a variety of grass and broadleaf weeds. The sulfonylureas inhibit acetolactate synthase, a plant enzyme required for the biosynthesis of branched-chain amino acids. Resistance to sulfonylurea herbicides lies in the rapidity with which a plant is able to metabolize the active ingredient into non-active compounds; thus, application timing can be critical to the control of certain weed species.

As UpBeet, triflusulfuron-methyl is currently registered for use on sugar beets; there are no other registered use sites for triflusulfuron-methyl (REFS, 1/23/02). UpBeet is a water-dispersible granule formulation containing 50% (by weight) triflusulfuron-methyl. For sugar beet, UpBeet may be broadcast applied via ground or air equipment at up to 0.032 lb ai/A/application. Multiple applications can be made at 5-10 day intervals with the total application not to exceed 0.078 lb ai/A/season. For chicory, two applications may be made, at 0.024 lb ai/A and at 5- to 10-day intervals, for a maximum seasonal application rate of 0.048 lb ai/A. This formulation may also be band-applied at rates equivalent to the broadcast rates (actual band rates are dependent upon crop row spacing). UpBeet is not to be applied via any type of irrigation system. The label for UpBeet lists a pre-harvest interval (PHI) of 60 days for both sugar beet and chicory, representing a potential mid-season use. Plant-back intervals are 0 days for sugar beets, 14 days for all other crops except corn, and 21 days for corn. A plant-back interval has not been proposed for chicory. HED is satisfied with the 14-day interval that chicory receives from being in the "other crop" category as listed on the current label.

4.2 Dietary Exposure

4.2.1 Residue Profile

Time-limited tolerances for residues of triflusulfuron-methyl *per se* in/on sugar beet roots and tops are listed in 40 CFR 180.492 at 0.05 ppm for each commodity. These tolerances are based on acceptable crop field trials in which residues were consistently below the limit of detection. The parent compound is the only chemical of concern for risk assessment. In plants, triflusulfuron-methyl undergoes cleavage of the sulfonylurea bridge to form triazine urea and ester sulfonamide. This cleavage occurs readily in soil and on the leaf surface, leaving no measurable residues of parent in sugar beets (whole plant) after 7 days post treatment. No tolerances are required on the processed commodities of sugar beets or in livestock commodities.

An adequate tolerance enforcement method is available in PAM II. The method extracts residues of triflusulfuron-methyl in a buffered acetonitrile solution, cleans the extract on a phenyl solid-phase extraction cartridge, and quantitates residues on a HPLC/UV system.

The chronic dietary exposure assessment is based on tolerance-level residues, assumptions of 100% crop treated, and consumption patterns as reported by respondents in the USDA's 1989-1992 Continuing Surveys of Food Intake by Individuals (CSFII) and should be considered a conservative estimate of exposure to triflusulfuron-methyl via dietary pathways (M. Doherty, D260469, 8/28/00). Because suitable data depicting residues of triflusulfuron-methyl in drinking water were not available for incorporation into the dietary exposure model, the dietary exposure estimates do not include potential exposure from drinking water.

4.2.2 Acute

There are no effects attributable to a single, oral dose of triflusulfuron-methyl. At the time the dietary exposure analysis was performed, there were a dose and endpoint for assessing acute exposure to females aged 13-50 years. In a meeting on 11/20/2001, the HIARC determined that no toxicological effects were attributable to a single exposure and that an acute dietary risk assessment is not required.

4.2.3 Chronic

The estimated chronic dietary exposures and risks are summarized in Table 4. For the general U.S. population and all population subgroups, the estimated chronic risk is <1% of the cPAD, which is well below HED's level of concern (100% of the cPAD). The dietary assessment conducted for PP#4F4278 did not include chicory in its residue profile (M. Doherty, D260469, 8/28/00). A subsequent assessment that would include chicory has not been requested because chicory was not reported as being consumed in the 1989-1992 CSFII. Therefore, inclusion of chicory in the dietary analysis would not alter the exposure or risk estimates from those obtained previously.

Table 4. Summary of Tier 1 Acute and Chronic Dietary Exposure Analyses.				
Population Subgroup	Acute Estimates		Chronic Estimates	
	Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% cPAD
General U.S. Population	NA	NA	0.000011	< 1%
Females aged 13-50 years	NA	NA	0.000009	< 1%
Infants aged < 1 year	NA	NA	0.000040	< 1%
Children aged 1-6 years	NA	NA	0.000025	< 1%
Children aged 7-12 years	NA	NA	0.000019	< 1%

4.2.4 Cancer

Triflusulfuron-methyl has been designated a Category C "possible human carcinogen." As such, the chronic exposure assessment is believed to be sufficiently protective of human health.

4.3 Water Exposure

Triflusulfuron-methyl is a non-persistent compound. While its low adsorption coefficients and potentially high water solubility indicate that it may leach to groundwater, its short half-life suggests that it will not accumulate in either surface or ground water, even after repeated applications. The only residue of concern in drinking water is parent triflusulfuron-methyl. As monitoring data for triflusulfuron-methyl in drinking water are not available, the Environmental Fate and Effects Division has supplied HED with Estimated Environmental Concentrations (EECs) which are Tier II estimates from the PRZM/EXAMS model for surface water residues and Tier I estimates from the SCI-GROW model for ground water residues. The EECs are based on an agricultural setting of sugar beets grown in Minnesota. Based on this use pattern, environmental conditions, and the physicochemical characteristics for triflusulfuron-methyl, the EECs for triflusulfuron-methyl are 0.42 µg/L (acute) and 0.005 µg/L (long-term average) in surface water and 0.50 µg/L in groundwater (acute and long-term). As part of the aggregate risk assessment (Section 5), these values are compared to back-calculated Drinking Water Levels of Comparison (DWLOCs) to estimate whether exposure through drinking water is likely to result in unacceptable aggregate exposure.

4.4 Residential Exposure

There are no current or pending uses for triflusulfuron-methyl that would result in non-occupational, non-dietary (i.e., "residential") exposure. Determination of aggregate risk does not include this pathway of exposure at this time. 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 ground application methods. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop

the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new data base submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard air-blast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

5.0 Aggregate Risk Assessments and Risk Characterization

Since there are no non-dietary, non-occupational pathways of exposure for triflusulfuron-methyl at this time, only dietary (food + water) pathways of exposure are incorporated into the aggregated risk estimates for this herbicide. Additionally, because only the dietary pathways are being considered, short- and intermediate-term aggregate risk assessments are not needed. The chronic aggregate risk is based on conservative, Tier 1 dietary (food only) exposure estimates. The resulting DWLOCs (TAble 5) are compared against Tier II (surface water) and Tier I (ground water) EECs. Overall, the aggregate risk assessments should be viewed as conservative and likely overestimate risk to the various population subgroups. Even without further refinement, the aggregate risk estimates are less than HED's level of concern. HED is not aware of any human health considerations that would preclude establishing tolerances for residues of triflusulfuron-methyl in/on chicory at 0.050 ppm, or converting the established time-limited tolerances for residues of triflusulfuron-methyl in/on sugar beet commodities (0.050 ppm) into permanent tolerances.

Table 5. Acute and Chronic Drinking Water Levels of Comparison

Population Subgroup	PAD, mg/kg/day	Aggregate Exposure, mg/kg/day	Maximum Allowable Water Exposure, mg/kg/day[A]	Surface Water EEC, µg/L	Ground Water EEC, µg/L	DWLOC, µg/L[B]
Acute Exposure						
An acute risk assessment is not required for triflusulfuron-methyl						
Chronic Exposure						
General U.S. Population	0.024	0.000011	0.023989	0.005	0.50	840
Females (13-50 years)	0.024	0.000009	0.023991	0.005	0.50	720
All Infants (<1 year)	0.024	0.000040	0.023960	0.005	0.50	240
Children (1-6 years)	0.024	0.000025	0.023975	0.005	0.50	240
Children (7-12 years)	0.024	0.000019	0.023981	0.005	0.50	240

[A] Maximum Allowable Water Exposure = PAD - Aggregate Exposure

[B] DWLOC = Maximum Allowable Water Exposure × 1000 µg/mg × Body Weight ÷ Consumption; DWLOCs are rounded to two significant figures.

5.1 Acute Risk

There are no effects attributable to a single, oral dose of triflusulfuron-methyl. An acute aggregate risk assessment is not required.

5.2 Chronic Risk

5.2.1 Chronic DWLOC Calculations

To calculate the chronic DWLOC, HED has used the standard body weights and water consumption of 70 kg and 2 L/day for the general population and adult males, 60 kg and 2 L/day for adult females, and 10 kg and 1 L/day for infants and children. The DWLOC equation is given in the footnotes of Table 5. For the representative populations, chronic DWLOCs range from 240 to 840 µg/L and are three orders of magnitude greater than the chronic ground water EEC, which is the worst-case EEC for drinking water (Table 5).

5.2.2 Chronic Aggregate Risk Assessment

Based on conservative assumptions regarding residue levels in food and drinking water, which are the only potential pathways of chronic exposure, chronic aggregate risk estimates are below HED's level of concern for the general U.S. population and all population subgroups, including those of infants and children.

5.3 Cancer Risk

Triflusulfuron-methyl has been designated a Category C "possible human carcinogen" and does not require a separate cancer risk assessment. The chronic aggregate risk assessment is sufficiently protective of human health.

6.0 Cumulative Risk

EPA does not have, at this time, available data to determine whether triflusulfuron-methyl has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. For the purposes of this tolerance action, EPA has not assumed that triflusulfuron-methyl has a common mechanism of toxicity with other substances. At such time as the Agency has a scientific basis for evaluating cumulative risk, the petitioner must submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate cumulative risk issues for triflusulfuron-methyl. At that time, the Agency will determine whether any tolerances for triflusulfuron-methyl need to be modified or revoked.

7.0 Occupational Exposure

Since no chemical-specific data for assessing human exposures during pesticide handling activities were submitted to the Agency in support of the registration of triflusulfuron-methyl,

HED used surrogate data from the Pesticide Handlers Exposure Database (PHED) Version 1.1. Defaults established by the Health Effects Division (HED) Science Advisory Council for Exposure were used for acres treated per day, body weight, and the level for personal protective equipment worn by handlers.

Toxicological endpoints from the HED's Hazard Identification Assessment Review Committee (HIARC) revisit (12/19/01) report were used to assess risk. No systemic toxicity was seen in rabbits at the limit dose following dermal applications for 21 days. No developmental concern (toxicity) was seen in the developmental toxicity studies with rats or rabbits. No dermal hazard was identified, therefore, quantification of dermal risk is not required; furthermore, the proposed use is not expected to result in exposures beyond short-term duration. For inhalation risk, the HIARC recommended use of the oral NOAEL of 7.1 mg/kg/day from the 90-day rat study. All occupational exposure estimates are based on the use of triflusufuron-methyl on sugar beets, which has a higher use rate than the proposed use on chicory.

The proposed product label, UpBeet Herbicide, has a 4-hour restricted entry interval (REI). Acute toxicity information is available for the technical which indicates that all six acute toxicity tests have been classified as Category III or IV (Table 2). Based on toxicity information on the active ingredient Triflusulfuron-methyl, it is a candidate for a 4-hour REI. However, in order for a 4-hour REI to be accepted by the EPA, the registrant must submit toxicity information on the end-use product and must provide a certification to the Agency regarding postapplication incidents. PR Notice 95-3 provides details on the process of applying for a 4-hour REI.

7.1 Occupational Handler

Inhalation MOEs for handlers are summarized in Table 6. With the exception of aerial applicators, handler inhalation MOEs were calculated at the baseline level (no respirator) and are greater than the target value of 100 and, therefore, do not exceed HED's level of concern. For aerial applicators, inhalation MOEs calculated using engineering controls (closed cockpit, no respirators) are also greater than the target value of 100 and, likewise, do not exceed HED's level of concern.

Table 6. Summary of Occupational Mixer/Loader/Applicator Margins of Exposure for Triflusulfuron-methyl.

Exposure Scenario	Mitigation Level	Inhalation Unit Exposure (µg/lb ai)	Crop	Application Rate (lb ai/A)	Amount Treated (A/day)	Inhalation Dose (mg/kg/day)	Inhalation MOE*
Mixer/Loader							
Dry Flowables Groundboom application	Baseline	0.77	Sugar Beets	0.032	80	0.000028	250,000
Dry Flowables Aerial application	Baseline	0.77	Sugar Beets	0.032	350	0.00012	59,000
Applicator							
Sprays Groundboom (open cab) application	Baseline	0.74	Sugar Beets	0.032	80	0.000027	260,000

Exposure Scenario	Mitigation Level	Inhalation Unit Exposure (µg/lb ai)	Crop	Application Rate (lb ai/A)	Amount Treated (A/day)	Inhalation Dose (mg/kg/day)	Inhalation MOE*
Sprays Aerial application	Engineering Controls	0.068	Sugar Beets	0.032	350	0.000011	650,000
Flagger							
Flagging Aerial Application	Baseline	0.35	Sugar Beets	0.032	350	0.000056	127,000

* Inhalation MOE = 7.1 mg/kg/day ÷ Inhalation Dose.

The handler exposure estimates in this assessment are based on a central tendency estimate of unit exposure and an upper-percentile assumption for the application rate, and are assumed to be representative of high-end exposures. The uncertainties associated with this assessment stem from the use of surrogate exposure data (e.g., differences in use scenario and data confidence) and assumptions regarding the amount of chemical handled.

7.2 Occupational Postapplication

Since the hazard associated with dermal exposure to triflusulfuron-methyl is negligible, risks associated with postapplication activities are not of concern.

8.0 Data Needs/Label Requirements

- In order to have a 4-hour REI, the petitioner must provide toxicity information on the end-use product and a certification to the Agency regarding postapplication incidents. PR Notice 95-3 provides details on the process of applying for a 4-hour REI. Alternatively, the label may be modified to specify a 12-hour REI.

- A 28-day inhalation (nose only) toxicity study is needed. Receipt of this study should be made a condition of registration.

cc: S. Williams-Foy, S. Wang, M. Doherty, RAB2 Reading File

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Chemical:	**Benzoic acid, 2-(((((4-(dimethylamino)-6**
PC Code:	**129002** 14000 Risk Review
HED File Code	**11000 ~~Chemistry Reviews~~**
Memo Date:	**02/12/2002**
File ID:	**DPD260076**
Accession Number:	**412-02-0281**

HED Records Reference Center
05/10/2002