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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

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OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
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Memorandum

Date: 13-December-2000

Subject: PP# 1F4032. **Ethametsulfuron methyl (Muster) in/on Canola. HED Risk Assessment.** PC Code 129091. DP Barcode's D238899, D245957, and D277062.

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Dupont is requesting a Section 3 registration and establishment of a tolerance to support the application of the herbicide, Ethametsulfuron methyl (Muster); EPA Reg 352-LLI, in/on canola. A summary of the findings from the proposed use and an assessment of human health risk resulting from the proposed use for ethametsulfuron are provided in this document.

1.0 Executive Summary

Ethametsulfuron-methyl is a new sulfonylurea class herbicide. It acts by inhibiting the enzyme acetolactate synthase, which is involved in the biosynthesis of branched-chain amino acids. It currently has no established U.S. tolerances or registered uses (of any kind) and no Codex, Canadian, or Mexican maximum residue limits.

The petitioner of ethametsulfuron methyl, DuPont, is proposing to use the herbicide on canola. The use would entail a single, early postemergence application of up to 0.019 lb ai/A. It would be a broadcast foliar spray using ground equipment. Field trials show that this use does not result in a quantifiable residue (limit of quantitation, 0.02 ppm), even when applied at an exaggerated rate (up to 3.3x). **A revised Section F is requested which will decrease the proposed tolerance (0.1 ppm) to 0.02 ppm.**

Ethametsulfuron-methyl is of relatively low acute toxicity with an oral LD_{50} of >5000 mg/kg and a dermal LD_{50} of >2000 mg/kg. No systemic toxicity was seen at the highest dose tested in subchronic toxicity studies in mice, rat and dogs (i.e, a LOAEL was not established). No evidence of chronic toxicity or carcinogenicity was seen in mice and rats; however, the dose levels tested in these studies were determined to be inadequate. It is noted, however, that other sulfonylurea herbicides do not show evidence of carcinogenicity or mutagenicity. In dogs, following oral administration for one-year, systemic toxicity was limited to decreases in body weight and body weight gains in males. There is no evidence of developmental toxicity either in the rat or rabbit following *in utero* exposure. In the rat, there is developmental toxicity at levels where maternal toxicity is present. There is no evidence of reproductive toxicity.

The Hazard Identification Assessment Review Committee only selected a chronic dietary endpoint for estimation of risk. The chronic endpoint is based on effects in the 2-generation reproduction study in rats with a NOAEL of 449 mg/kg/day. At the study LOAEL of 1817 mg/kg/day decreased body weight and body weight gain in parental animals was observed. The chronic RfD is 4.5 mg/kg/day (UF = 100). Based on an FQPA SF of 1 (discussed in detail below), the chronic population adjusted dose (cPAD) for use in risk assessment is 4.5 mg/kg/day. No appropriate endpoints for acute dietary, short-, intermediate-, and long-term dermal and inhalation exposures were identified. In addition, the vapor pressure of ethametsulfuron methyl is low, thus limiting the inhalation exposure potential to handlers and other occupationally exposed workers.

The FQPA Safety Factor Committee concluded that the FQPA safety factor could be removed for ethametsulfuron-methyl because the toxicology database is complete; there is no indication of quantitative or qualitative increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure; unrefined dietary exposure estimates are protective since they will exaggerate dietary exposure estimates; EFED provided ground and surface source drinking water exposure assessments, resulting in estimates that are conservative upper-bound concentrations; and there

are currently no registered residential uses for ethametsulfuron-methyl and therefore, non-dietary, non-occupational exposure is not expected.

The HED Metabolism Assessment Review Committee (MARC) has determined that the regulable residue in plant commodities is parent compound only. Further the committee determined that the residue of concern in plants and drinking water for risk assessment purposes is also parent compound only. Animal metabolism studies to support the use on canola have been waived by the HED Chemistry Science Advisory Committee as there is not likely to be detectable residues in animal commodities as a result of the proposed use.

The proposed HPLC analytical enforcement method is not acceptable. For the determinative step, the method utilizes a photoconductivity detector which is no longer commercially available. A revised method with a replacement means of detection is required. The revised method will need to successfully undergo both independent and in-house (ACB/BEAD) method validation trials. Limited testing of ethametsulfuron-methyl by FDA multiresidue protocol C reportedly produced greater than 50% full scale deflection for several column/detector combinations. This level of response does not appear to be sufficient for use as an enforcement alternative.

Several data gaps remain to be addressed in the product chemistry data submitted. Currently the product chemistry data and resolution of the outstanding data requirements are under the purview of RD. HED does not believe these data gaps impact the human health risk assessment.

This risk assessment considers dietary exposure through the food and drinking water. Occupational exposure is also considered. Workers may be exposed to ethametsulfuron-methyl during mixing, loading, application and postapplication activities. Based on the proposed application rates and use scenarios, short- and intermediate-term exposures may occur. Chronic exposure (6 or more months of continuous exposure) is not expected. There are currently no residential uses of ethametsulfuron methyl, therefore, residential exposure assessments are not included in this risk assessment.

Since no endpoints for dermal toxicity were identified by the HIARC and exposure via inhalation is expected to be low, risk assessments for occupational exposure were not conducted and are not required to support the requested registration.

The chronic dietary risk assessment incorporated the pending tolerance level residues (0.02 ppm) and 100% crop treated (CT) to estimate the exposure for the general population and subgroups of interest. **All of the estimated chronic dietary exposures are less than 1% of the cPAD and are below HED's level of concern.**

The estimated environmental concentrations (EECs) for drinking water derived from ground water were approximated using SCI-GROW (Screening Concentrations in Ground Water). For

canola, the ground water EECs for use in the human health risk assessment are estimated to be 0.11 µg/L for both the peak (acute) and yearly average (chronic). The EECs for drinking water derived from surface water were approximated using PRZM/EXAMS. These EECs are estimated to be 0.481µg/L for the peak (acute) and 0.324 µg/L for the yearly average (chronic). Since HED does not have sufficient data to quantitatively incorporate exposure to ethametsulfuron-methyl from residues in drinking water, HED has estimated drinking water levels of comparison (DWLOCs) and compared them to the EECs. For the chronic aggregate risk, all of the DWLOCs for all population subgroups are greater than the EECs. **The DWLOCs range from 45,000 to 160,000 µg/L. Therefore, the chronic aggregate risks are below HED's level of concern.**

Data gaps

Toxicology: The petitioner should conduct a General Metabolism study (§85-1, §870.7485) according to the 1996 guidelines and registration of this chemical for the canola use should be conditional on the submission of the metabolism study.

Product Chemistry: Several product chemistry data gaps remain to be addressed: OPPTS GLN 830 Series: Product Properties. Additional data are necessary to fulfull the requirements of 61-1 through 61-3, 62-1, 62-3, 3-13, 63-14, 63-16, 63-17, and 63-20. In addition, the proposed enforcement method is not suitable as currently written.

Residue Chemistry: The proposed analytical enforcement method utilizes a (photoconductivity) detector which is no longer commercially available. Thus, DuPont (petitioner) needs to revise this method to provide a replacement means of detection. The revised method will need to successfully undergo both an independent laboratory validation trial and an in-house method validation trial conducted by ACB/BEAD (OPPTS GLN 860.1340). In addition, a revised Section F needs to be submitted which proposes the tolerance for residues of ethametsulfuron-methyl in/on canola seed at 0.02 ppm (rather than the currently proposed 0.1 ppm) (OPPTS GLN 860.1550).

Tolerances Recommendation Although this human health risk assessment supports the establishment of a 0.02 ppm tolerance for residues of ethametsulfuron-methyl in/on canola seed, HED notes that **there is no analytical enforcement method available to enforce such a tolerance** until the method is revised with a replacement means of detection, and then successfully undergoes independent and in-house laboratory validation trials.

2.0 Physical/Chemical Properties Characterization

CAS chemical name: methyl 2-[[[[[4-ethoxy-6-(methylamino)-1,3,5-triazin-2-yl]amino]carbonyl] amino]sulfonyl]benzoate

CAS registry no.: 97780-06-8

Common name: ethametsulfuron-methyl

Other name(s): DPX-A7881

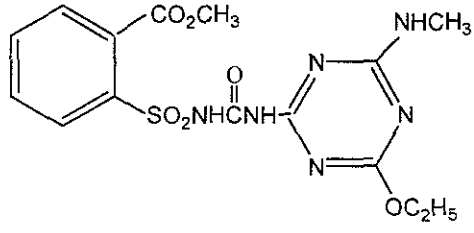
Trade name: Muster® Herbicide

Chemical class: sulfonylurea herbicide

Molecular formula: $C_{15}H_{18}N_6O_6S$

Molecular weight: 410.4

Chemical structure:



Isomeric forms: none

Impurities: polar and non-polar nitrosamines were not detected (LOD, 0.1 ppm) in the technical product. (Five batches were analyzed using validated GC/TEA and NPLC/TEA methods with comparison against known standards.)

Risk Assessment Information: The vapor pressure of ethametsulfuron-methyl is low, thus limiting the inhalation exposure potential to handlers (mixer/loader/applicators) and other occupationally exposed workers. The exposure potential of non-occupational persons is essentially nil, as there are no residential or recreational use sites proposed or registered for this chemical and the label specifies spray drift precautions.

A summary of the physical/chemical properties for ethametsulfuron is contained in the table below.

Physical/Chemical Properties of Ethametsulfuron-Methyl	
Color	white
Physical state	crystalline solid
Odor	odorless
Melting point	194° C; does not decompose on melting
Boiling point	N/A; ethametsulfuron-methyl is a solid
Density	1.60 g/cc
Solubility	matrix — solubility (mg/L) at 25° C water (pH 6.3) — 1.8 buffer (pH 5) — 8 buffer (pH 7) — 350 buffer pH 9) — > 1450 acetone — 1600 acetonitrile — 830 ethanol — 170 hexane — < 5 isopropanol — 74 methanol — 350 methylene chloride — 3900 toluene — 9 xylene — 10 ethyl acetate — 680
Vapor pressure	5.8×10^{-15} mm Hg at 25° C
Dissociation constant	pKa = 4.6
Octanol/Water Partition Coefficient	log K_{ow} (at 25° C) = 0.89 at pH 7 = 38.7 at pH 5
pH	4.2 (at 25° C, 1% w/v slurry) 4.9 (at 25° C, 5% w/v slurry)
Stability	decomposes at 230° C

3.0 Hazard Characterization

3.1 Hazard Profile

The toxicity data indicate that ethametsulfuron methyl has low acute oral, dermal and inhalation toxicity. It is neither a skin sensitizer nor skin irritant. It is irritating to the cornea, but clear by Day 10. No systemic toxicity was seen at the highest dose tested in subchronic toxicity studies in mice, rat or dogs (i.e, a LOAEL was not established).

No evidence of chronic toxicity or carcinogenicity was seen in mice and rats; however, the dose levels tested in these studies were determined to be inadequate to assess toxicity or carcinogenic potential. However, it is noted that other sulfonylurea herbicides do not show evidence of

carcinogenicity or mutagenicity. In dogs, following oral administration for one-year, systemic toxicity was limited to decreases in body weight and body weight gains in males.

There is no evidence of increased susceptibility in the rat or rabbit fetuses following *in utero* exposure or in the fetuses following pre-and post natal exposure in the two-generation reproduction study. Developmental effects in both species (rats and rabbits) were seen at a dose that is four times the limit dose and effects in the offsprings were seen only at the limit dose.

Ethametsulfuron methyl was negative for inducing mutations in all acceptable guideline studies of the standard battery of mutagenicity tests.

Although a metabolism study was performed. The study had many deficiencies and was determined to be unacceptable. An acceptable metabolism study is required as a condition of registration.

Table 1. Acute Toxicity of Ethametsulfuron methyl technical.

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
870.1100	Acute Oral- Rats	42022132	LD50 > 5 g/kg	IV
870.1200	Acute Dermal- Rats	42022134	LD50 > 2 g/kg	III
870.1300	Acute Inhalation- Rats	42022136	LC50 > 5.7 mg/L	IV
870.2400	Primary Eye Irritation- Rabbits	42022138	Corneal irritation clearing by Day 10	II
870.2500	Primary Skin Irritation- Rabbits	42022140	Non-irritant	IV
870.2600	Dermal Sensitization- Guinea pigs	42022142	Non sensitizer	N/A

Table 2. Toxicity Profile of Ethametsulfuron methyl Technical.

Guideline No./ Study Type	Results
870.3100 90-Day oral toxicity rats	NOAEL = 365/453 mg/kg/day (m/f) HDT LOAEL = not determined; supplementary due to lack of a toxic response (inadequate dose levels).
870.3100 90-Day oral toxicity in mice	NOAEL = > 686/916 mg/kg/day (m/f) HDT LOAEL = not determined
870.3150 90-day oral toxicity in dogs	NOAEL = >390/383 mg/kg/day (m/f) LOAEL = not determined; lack of a toxic response (inadequate dose levels).
870.3700a Prenatal developmental in rats	**Maternal** NOAEL = 1000 mg/kg/day LOAEL = 4000 mg/kg/day based on decr. BW, decr. FC **Developmental** NOAEL = 1000 mg/kg/day LOAEL = 4000 mg/kg/day based on reduced fetal BWG, increased skeletal variations
870.3700b Prenatal developmental in rabbits	**Maternal** NOAEL = 250 mg/kg/day LOAEL = 1000 mg/kg/day based on increased relative liver wt. **Developmental** NOAEL = 1000 mg/kg/day LOAEL = 4000 mg/kg/day based on increased resorptions (early fetal death), decreased litter size
870.3800 Reproduction and fertility effects	**Parental/Systemic** NOAEL = 395/449 mg/kg/day (m/f) LOAEL = 1582/1817 mg/kg/day (m/f) based on reduced body weight and body weight gain in P & F1a males and females. **Reproductive** NOAEL = 1582/1817 mg/kg/day (m/f) at HDT LOAEL = not determined
870.4100b Chronic toxicity dogs	NOAEL = 87.3/86.9 mg/kg/day (m/f) LOAEL = 478/483 mg/kg/day (m/f) based on reduced body weight, body weight gain, and food efficiency, decrease in mean serum values
870.4200 Carcinogenicity mice	NOAEL = 705/930 mg/kg/day LOAEL = not determined **no evidence of carcinogenicity at doses inadequate to assess carcinogenic potential.**
870.4300 Comb. Chronic/Carcinogenicity rats	NOAEL = 210/267 mg/kg/day LOAEL = not determined **no evidence of carcinogenicity at doses inadequate to assess carcinogenic potential.**
870.5300 Gene Mutation	In vitro gene mutation in CHO cells. Negative for mutagenicity.

Guideline No./ Study Type	Results
870.5395 Gene Mutation	In vivo micronucleus assay in mice did not induce bone marrow toxicity.
870.5300 Gene Mutation	In vivo rat bone marrow assay did not indue a clastogenic response.
870.550 Gene mutation	In vitro UDS assay did not induce a genotoxic effect.
870.5100 Gene mutation	S. typhimurium/ mammalian microsome assay did not induce a genotoxic effect.
870.7485 Metabolism and pharmacokinetics	**Submitted study is Unacceptable.** New study required as a condition of registration.
870.7600 Dermal penetration	No studies available. Not required since a dermal risk assessment is not required.

3.2 FQPA Considerations

The Hazard Identification Assessment Review Committee (HIARC) determined that the available Agency Guideline studies indicated no increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure to ethametsulfuron. In the prenatal developmental toxicity studies in rats and rabbits and the two-generation reproduction study in rats, toxicity to the fetuses/offspring, when observed, occurred at equivalent or higher doses than in the maternal/parental animals.

The FQPA Safety Factor Committee recommended that the 10x factor for protection of infants and children (as required by FQPA) be removed since: 1) the toxicology data base is complete; 2) there is no indication of increased susceptibility of rats or rabbit fetuses to *in utero* and/or postnatal exposure in the developmental and reproductive toxicity data; 3) unrefined dietary exposure estimates are protective since they will exaggerate dietary exposure estimates; 4) EFED will model ground and surface source drinking water exposure assessments, resulting in estimates that are conservative upper-bound concentrations; and 5) there are currently no registered residential uses for ethametsulfuron and therefore, non-dietary exposure to infants and children is not expected.

3.2.1 Cumulative Risk

EPA does not have, at this time, available data to determine whether ethametsulfuron 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, therefore, EPA has not

assumed that ethametsulfuron methyl has a common mechanism of toxicity with other substances.

On this basis, 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 issues related to whether ethametsulfuron methyl shares a common mechanism of toxicity with any other substance and, if so, whether any tolerances for ethametsulfuron methyl need to be modified or revoked.

3.2.2 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 bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

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

3.3 Dose Response Assessment

An acute RfD (aRfD) was not established because a dose and endpoint attributable to a single exposure were not identified from the available oral toxicity studies, including maternal toxicity in the developmental toxicity studies.

The chronic reference dose (cRfD) of 4.5 mg/kg/day was determined on the basis of a 2-generation reproduction study in rats. In the 2-generation reproduction study, toxicity (decreases in body weight and body weight gain in the parental animals and in the F1a and F1b generations) was seen at doses (1582/1817 mg/kg/day in males/females) which were above the Limit-Dose with the NOAEL at 449/395 mg/kg/day). In deliberations on the endpoint, the HIARC considered the findings in the chronic dog study to assess if the dog or the rat was the most sensitive species. However, when the committee took into account the wide spread in the doses tested in the chronic dog study, the results of the 2-generation reproduction study, and the results

of the subchronic studies, a weight-of-evidence approach indicated that the true no effect level in both species appear to be an approximately dose of 400 mg/kg/day. Therefore, the HIARC selected a dose of 449 mg/kg/day from the 2-generation reproduction study to derive the chronic RfD. **Based on the NOAEL of 449 mg/kg/day and applying a 100-fold uncertainty factor, the cRfD is 4. 5 mg/kg/day. The FQPA safety factor of 1x is applicable for chronic risk assessment. Thus the cPAD is equivalent to the cRfD and is 4.5 mg/kg/day.**

Carcinogenicity: The carcinogenic potential of ethametsulfuron could not be evaluated since the highest dose tested in mice and rats did not elicit systemic toxicity and thus was judged to be inadequate to assess the carcinogenic potential of ethametsulfuron. No rationale was provided for dose selection. In addition, no systemic toxicity was seen either in the subchronic toxicity study mice (NOAEL=686 and 916 mg/kg/day in males and females, respectively) or in the subchronic toxicity study in rats (NOAEL= 365 and 453 mg/kg/day in males and females, respectively). However, the HIARC noted that ethametsulfuron, sulfonylurea is structurally-related to other sulfonylureas such as bensulfuron methyl (PC Code. 128820), halosulfuron methyl (PC Code.128721), nicosulfuron (PC Code 129008), primisulfuron methyl (PC Code 128973) and rimsulfuron (PC Code 129009). Of the 5 compounds listed, halosufluron methyl, nicosulfuron, and rimsulfuron are classified as a Group E (no evidence of carcinogenicity) chemical and primisulfuron methyl is classified as a Group D (not classifiable as to human carcinogenicity) chemical. Therefore, a quantitative risk assessment is not warranted.

Mutagenicity: Ethametsulfuron methyl was negative for inducing mutations in a standard battery of mutagenicity studies which included: *in vitro* UDS assay, *in vitro* CHO assay, *in vivo* bone marrow assay, and a *S. typhimurium* microsome assay.

Based on the findings of the HIARC with respect to carcinogenicity and mutagenicity, a quantitative risk assessment for cancer risk is not required to support the requested use.

Dermal Penetration: No dermal absorption studies are available and no dermal absorption values can be estimated from the available data base. Data are not required as a dermal risk assessment is not required for this chemical.

Dermal and inhalation toxicity: The vapor pressure and water solubility of ethametsulfuron methyl are low, thus limiting the inhalation and dermal exposure potential to handlers and other occupationally exposed workers. The dermal toxicity study in rats was waived based on lack of systemic toxicity in oral toxicity studies, thereby making the potential for risk from short- or intermediate-term dermal exposure negligible. In addition, long-term exposure via the dermal or inhalation route is not expected based on the current use pattern. Therefore no endpoints were selected for exposure scenarios by the dermal or inhalation routes.

The doses and toxicological endpoints selected for various exposure scenarios are summarized in the table below.

Table 3. Summary of Toxicological Dose and Endpoints for Ethametsulfuron methyl for Use in Human Risk Assessment

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF* and Endpoint for Risk Assessment	Study and Toxicological Effects
Acute Dietary	A dose and endpoint were not selected because there were no effects observed in oral toxicology studies including maternal toxicity in the developmental toxicity studies in rats and rabbits that are attributable to a single exposure (dose).		
Chronic Dietary	NOAEL= 449 mg/kg/day UF = 100x **Chronic RfD** = 4.5 mg/kg/day	FQPA SF = 1x **cPAD** = 4.5 mg/kg/day	2-Generation reproduction study in rats LOAEL = 1817 mg/kg/day based on decreased body wt. and body wt. gain in parental animals and F1a and F1b generations.
Short-, Intermediate and Long Term Dermal	No endpoints were selected for exposure scenarios by the dermal route, since the dermal toxicity study in rats was waived based on lack of systemic toxicity in oral toxicity studies, thereby making the potential for risk negligible.		
Inhalation (any time period)	Based on the low toxicity, use pattern and method of application, there is no concern for potential exposure/risk via this route.		
Cancer (oral, dermal, inhalation)	The carcinogenic potential of ethametsulfuron could not be evaluated since the highest dose tested in mice and rats did not elicit systemic toxicity. However, the HIARC noted that ethametsulfuron, sulfonylurea is structurally-related to other sulfonylurea herbicides do not show evidence of carcinogenicity or mutagenicity. Therefore, a quantitative risk assessment is not warranted.		

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

4.0 Exposure Assessment

4.1 Summary of Registered Uses

Use Pattern Information

Ethametsulfuron-methyl is a new active ingredient (ai) of the sulfonylurea herbicide class. It controls and suppresses broadleaf weeds. It acts by inhibiting the enzyme acetolactate synthase, which is involved in the biosynthesis of branched-chain amino acids. There are currently no registered U.S. use sites (agricultural or non-agricultural) of any kind.

The proposed use under consideration is for early season postemergence weed control in canola. The formulated product, Muster® Herbicide (EPA Reg. No. 352-LLl), is a dry flowable

dispersible granular formulation containing 75% ai. A single, foliar broadcast application (0.3-0.4 oz of product; 0.23-0.30 oz ai; 0.014-0.019 lb ai) is to be applied per acre per growing season when young canola plants are actively growing, between the two leaf to bolting stage. Use ground equipment only and sufficient water (≥ 5 gpa) to achieve even coverage and canopy penetration. Include a non-ionic surfactant at 0.25% v/v. The specified minimum re-cropping interval is based on phytotoxic concerns to following crops, and ranges from 10-22 months, depending on the following crop to be planted. The growing region is ID, MN, MT, ND, OR, WA, and WY.

4.2 Dietary Exposure/Risk Pathway

4.2.1 Residue Profile

Background

There are currently no U.S. tolerances established for ethametsulfuron-methyl. The currently proposed use is on canola only. This risk assessment evaluates the proposed use on canola only.

The petitioner (DuPont) has proposed a tolerance for residues of ethametsulfuron-methyl per se in on canola seed at 0.1 ppm. However, HED considers that a tolerance of 0.02 ppm (limit of detection) is adequate and more appropriate. A revised Section F proposing a 0.02 ppm tolerance needs to be submitted.

No Codex, Canadian, or Mexican maximum residue limits are established for this chemical.

Residue Profile

The qualitative nature of the residue in canola has been adequately delineated based upon a canola metabolism study. The major components identified were parent ethametsulfuron-methyl and two metabolites (the O-deethyl and the N-demethyl-O-deethyl) containing the intact sulfonylurea bridge. The HED Metabolism Assessment Review Committee (MARC) has determined (memo, G. J. Herndon, 12/9/98, D251538) that the residue to be regulated in plant commodities (and used in risk assessments for plant commodities and for drinking water) is the parent compound only.

DuPont (petitioner) requested, and the HED Chemistry SAC has granted (memo, G. J. Herndon, 1/14/99, D237062), a waiver from the requirement to submit animal metabolism studies in support of the proposed use on canola. The basis for granting the waiver was the determination that there was no reasonable expectation of finite residues of ethametsulfuron-methyl in animal commodities as a result of the proposed use on canola [40 CFR 180.6(a)(3)], and no tolerances on animal commodities would be needed.

The data supporting the pending tolerance (0.02 ppm) on canola seed are from crop field trials. No quantifiable residues (LOQ, 0.02 ppm) of ethametsulfuron-methyl were reported in any canola seed sample following treatment at up to 3.3x the proposed label rate. Based on these exaggerated rate field trial data, no data or tolerances were required for the processed commodities.

DuPont submitted a proposed analytical enforcement method (MRID# 420221-13) which uses HPLC coupled with a photoconductivity detector. The Analytical Chemistry Branch (ACB)/BEAD was unable to validate this method as the photoconductivity detector is no longer commercially available (memo, M. Law, 12/14/99, D260698). Thus, DuPont needs to revise this method to utilize a replacement means of detection. The revised method will need to successfully undergo both an independent laboratory validation trial and an in-house method validation trial conducted by ACB/BEAD. Until that transpires, **HED considers that there is no adequate analytical method available to enforce the proposed tolerance in/on canola seed.**

Ethametsulfuron-methyl was tested through Protocol C of the FDA multiresidue testing procedures. Only minimal data and no chromatograms were submitted. Responses greater than 50% full scale deflection were reportedly produced for several column/detector combinations. Based on the limited information provided, this level of response does not appear to be sufficient for use as an enforcement alternative.

4.2.2 Dietary Exposure and Risk Analysis

HED conducts dietary (food only) risk assessments using DEEM™, which incorporates consumption data generated in USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1989-1992. For acute dietary risk assessments, one-day consumption data are summed and a food consumption distribution is calculated for each population subgroup of interest. The consumption distribution can be multiplied by a residue point estimate for a deterministic exposure/risk assessment, or be used with a residue distribution in a probabilistic type risk assessment. Acute exposure estimates are expressed in mg/kg bw/day and as a percent of the aPAD. For chronic risk assessments, residue estimates for foods or food-forms of interest are multiplied by the average consumption estimate of each food/food-form of each population subgroup. Chronic exposure estimates are expressed in mg/kg bw/day and as a percent of the cPAD.

A DEEM acute exposure analysis was not performed since an appropriate endpoint attributable to a single exposure was not selected.

A DEEM cancer risk analysis was not performed since a quantitative cancer risk assessment is not required to support this use.

A DEEM chronic exposure analysis was performed using the proposed tolerance level residues (0.02 ppm) and 100% CT to estimate the exposure for the general population and subgroups of interest. The % cPAD that would be above HED's level of concern would be 100%.

Table 4: Summary of Ethametsulfuron methyl DEEM™ Analysis

Subgroups	Exposure (mg/kg/day)	% cPAD[1]
U.S. population	0.000000	<1
All Infants (<1 year old)	0.000000	<1
Children (1-6 years old)	0.000000	<1
Females (13-50 years old)	0.000000	<1
Males (13-19 years old)	0.000000	<1

cPAD = 4.5 mg/kg/day

Based on the results of this analysis, exposure to ethametsulfuron methyl from food will utilize <1% of the cPAD for all population subgroups. Although the DEEM output expresses exposure as "0.000000" mg/kd/day, using the canola consumption values in DEEM and the tolerance of 0.02 ppm, the maximum chronic exposure is estimated to be 0.0000002 mg/kg/day for any population (children 1-6 years).

4.2.3 Water Exposure/Risk Pathway

EFED provided environmental fate and drinking water assessments for ethametsulfuron methyl (Memo, C. Laird, August 21, 2000, DP Barcode D259036).

4.2.3a Environmental Fate Assessment

Ethametsulfuron methyl is persistent in the environment under aerobic and anaerobic conditions and is highly mobile, therefore, it is very likely to reach surface water and ground water. Persistence, thus the extent of contamination, is affected by soil temperature and soil moisture, low temperatures and low moisture content of the soil significantly diminish the biotransformation of ethametsulfuron methyl. The canola growing area of the US has environmental characteristics that would likely increase the persistence of ethametsulfuron methyl.

4.2.3b Ground Water EEC

The EECs for drinking water derived from ground water were approximated using SCI-GROW (Screening Concentrations in Ground Water) (Barrett, 1997). SCI-GROW is a linear regression model based on data derived from Prospective Ground water Studies (PGW) completed by registrants for the USEPA. The annual application rate used for ethametsulfuron methyl (0.019

lbs. a.i. acre^{-1}) is the maximum recommended value for canola. Input parameter values used in SCI-GROW for ethametsulfuron methyl can be found in Appendix I. The K_{oc} value (62 L kg^{-1}) was the median value for all the soil types. The aerobic soil metabolic half-life (189 days) was the average of four values. The ground water concentration resulting from the SCI-GROW modeling is shown in Table 5. Since there is relatively little temporal variation in ground water compared to surface water, the concentrations can be considered as acute and chronic values.

SCI-GROW provides a ground water screening exposure value for use in determining the potential risk to human health from drinking ground water contaminated with pesticides. SCI-GROW estimates ground water concentrations for pesticides applied at the maximum allowable rate in areas where ground water may be vulnerable to contamination. However, the data used to develop SCI-GROW come from a limited number of PGWs which may not represent the conditions in the use areas for ethametsulfuron methyl. Also, SCI-GROW does not take into consideration many important variables which may have a significant impact on the potential for ethametsulfuron methyl to reach ground water. These include soil structure (preferential flow), soil moisture conditions, the amount of precipitation and the temporal relationship between application and precipitation events. As a consequence, concentrations observed in ground water may be higher or lower than those derived using SCI-GROW and actual monitoring data should be used to estimate environmental concentrations. When monitoring data are available we will evaluate their appropriateness for use in an exposure assessment.

Table 5. Ground water EECs (µg/ L) for use in the human health risk assessment.

Location/Crop	Peak (Acute)	Yearly Average (Chronic)
ND Canola	0.11	0.11

4.2.3c Surface Water EECs

The EECs for drinking water derived from surface water were approximated using PRZM/EXAMS. Table 6 provides the results to be used in the drinking water assessment. The farm pond was replaced with an index reservoir which more accurately represents a potential drinking water reservoir (Jones *et al*, 2000). The majority of the PRZM input values (Appendix I of EFED memo) are the same except the size of the treated area, the distance to the receiving water body and the percentage of applied pesticide which becomes spray drift. These were adjusted to represent the dimensions of the actual reservoir the index reservoir is based on. There were also changes to the EXAMS input values, most notably the geometry of the receiving water body. Also, the farm pond did not have any flow, whereas the index reservoir has flow, both into the and out of the reservoir. The flow is balanced and based on the average yearly runoff generated from the 36 years of precipitation data in the Major Land Resource Area

(MLRA) of the modeled scenario (North Dakota-MLRA 55A). A complete description of the Index Reservoir can be found in Jones, *et. al.*, 2000.

Table 6. Surface water EECs (µg/L) for use in the human health risk assessment.

Location/Crop	Peak (Acute)	Yearly Average (Chronic)
ND Canola	0.481	0.324

4.2.3d DWLOCs

A DWLOC is a theoretical upper limit on a pesticide's concentration in drinking water in light of total aggregate exposure to a pesticide in food, drinking water, and through residential uses.

HED does not have sufficient data to incorporate, quantitatively, exposure to ethametsulfuron-methyl from residues in drinking water. In order to address this route of exposure, HED has calculated Drinking Water Levels of Comparison (DWLOCs). The DWLOCs are compared to modeled concentrations of ethametsulfuron-methyl in surface and groundwater to determine if unacceptable residue levels are likely to be contributed via drinking water. EFED has performed a Tier 1 drinking water assessment for ethametsulfuron-methyl, using PRZM/EXAMS and SCI-GROW to provide estimated environmental concentrations in surface and ground water, respectively. Using conservative input parameters, the PRZM/EXAMS model estimates a peak (acute) ethametsulfuron-methyl concentration of 0.481 ppb and a 1-year average (chronic) concentration of 0.324 ppb in surface waters. Using similar input parameters, SCI-GROW estimates groundwater concentrations of not more than 0.11 ppb.

4.3 Residential Exposure/Risk Pathway

At present, there are no registered or proposed residential uses for ethametsulfuron methyl.

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 groundboom 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 airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift

management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

5.0 Aggregate Risk Assessments and Risk Characterizations

In determining aggregate risk, HED has examined acute, chronic, and cancer endpoint scenarios and included exposures from food and drinking water. Since there are no acute or cancer scenarios, only a chronic aggregate risk assessment was performed. No short- or intermediate-term risk assessments are required since no dermal or inhalation end points were selected. For chronic aggregate risk assessment, the calculated DWLOCs for all population subgroups are greater than EFED's EEC, as shown in Tables 7 and 8.

Table 7. Calculations of Drinking Water Levels of Comparisons for **Chronic** Exposure to Ethametsulfuron-methyl

Population Category	cPAD (mg/kg/day)	Food Exposure[1] (mg/kg/day)	Non-dietary Exposure	Max. Water Exposure[2] (mg/kg/day)	Body weight (kg)	Water consumed (L/day)	DWLOC [3] (μg/L)
US population	4.5	0.000000	N/A	4.5	70	2	160,000
Females 13+	4.5	0.000000	N/A	4.5	60	2	140,000
Infant and Children	4.5	0.000000	N/A	4.5	10	1	45,000

[1] Exposure from food from DEEM analysis

[2] Maximum Water Exposure (Chronic) (mg/kg/day) = cPAD (mg/kg/day) - Food Exposure (mg/kg/day).

[3] DWLOC(μg/L) = Max. water exposure (mg/kg/day) x body wt (kg) ÷ [(10^{-3} mg/μg) x water consumed daily (L/day)].

Table 8. Drinking Water Levels of Comparisons for **Chronic** Exposure to Ethametsulfuron-methyl					
Population Subgroup[1]	cPAD (mg/kg/day)	%cPAD [2] (Food)	Surface Water EEC [3] (ppb)	Ground Water EEC (ppb)	Chronic DWLOC [4] (μg/L)
U.S. Population	4.5	<1	0.32	0.11	160,000
Females 13+	4.5	<1	0.32	0.11	140,000
Infants and children	4.5	<1	0.32	0.11	45,000

[1] Within each of these categories, the subgroup with the highest food exposure was selected.
[2] % cPAD from Table 4.
[3] EEC: Estimated Environmental Concentration, chronic value.
[4] Chronic DWLOC from Table 7.

EPA has concluded that exposure to ethametsulfuron-methyl from food will utilize <1% of the cPAD for all population subgroups. There are no residential uses for ethametsulfuron-methyl that result in chronic residential exposure to ethametsulfuron-methyl. In addition, despite the potential for chronic dietary exposure to ethametsulfuron-methyl in drinking water, after calculating the DWLOCs and comparing them to conservative model estimated environmental concentrations of ethametsulfuron-methyl in surface and ground water, EPA does not expect the aggregate exposure to exceed 100% of the cPAD.

6.0 Occupational Exposure

Ethametsulfuron-methyl may be applied by ground equipment only. It is formulated as a dry flowable concentrate (75% a.i.) and applied at the maximum rate of 0.019 lbs a.i./acre for use on canola.

Workers may be exposed to ethametsulfuron methyl during mixing, loading, application and postapplication activities. Based on the proposed application rates and use scenarios, short- and intermediate-term exposures may occur. Chronic exposure (6 or more months of continuous exposure) is not expected.

Short- or intermediate-term dermal and inhalation endpoints were not identified by the Hazard Identification Assessment Review Committee. Dermal toxicity study in rats was waived based on lack of systemic toxicity in oral toxicity studies and thereby making the potential for risk from dermal exposure negligible. Based on the current use pattern (i.e.,1 application/season), long-term exposure via the dermal route is not expected and no endpoint was selected for long-term dermal exposure. In addition, the vapor pressure of ethametsulfuron methyl is low, thus

limiting the inhalation exposure potential to handlers and other occupationally exposed workers.

7.0 Data Needs/Label Requirements

7.1 Toxicology

870.4785 General Metabolism

7.2 Product Chemistry

OPPTS GLN 830 Series: Product Properties

Several product chemistry data gaps remain to be addressed. Additional data are necessary to fulfull the requirements of 61-1 through 61-3, 62-1, 62-3, 3-13, 63-14, 63-16, 63-17, and 63-20. In addition, the proposed enforcement method is not suitable as currently written.

7.3 Residue Chemistry

OPPTS GLN 860.1340: Residue Analytical Methods

The proposed analytical enforcement method utilizes a (photoconductivity) detector which is no longer commercially available. Thus, DuPont (petitioner) needs to revise this method to provide a replacement means of detection. The revised method will need to successfully undergo both an independent laboratory validation trial and an in-house method validation trial conducted by ACB/BEAD.

OPPTS GLN 860.1550: Proposed Tolerances

A revised Section F needs to be submitted which proposes the tolerance for residues of ethametsulfuron-methyl in/on canola seed at 0.02 ppm (rather than the currently proposed 0.1 ppm).

7.4 Re-entry interval

The acute toxicity classification for primary eye irritation of ethametsulfuron methyl is category II which requires a 24-hour REI. HED recommends that the Registration Division ensure that the registration label for Ethametsulfuron-methyl (Muster ® Herbicide) for use on canola be amended to specify a 24- hour REI.

References

1. HIARC, 9/12/98
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3. D269457, DEEM analysis, 10/23/2000
4. D259036, EFED Water Risk Assessment, 8/21/2000
5. D269822, ORE Assessment, 10/25/2000
6. D237044, Residue Chemistry Update, 2/2/99
7. D237062, Residue Chemistry, 1/14/99
8. D176331, Analytical Method and Residue Chemistry, 7/15/93
9. D260698, Residue Analytical method 12/144/99

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cc with attachments: RAB2 reading file

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