UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

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MEMORANDUM

SUBJECT: **Sulfometuron Methyl**: HED Chapter of the Reregistration Eligibility Decision Document (RED). PC Code: 122001, DP Barcode: 346064.

Regulatory Action: Phase 1 Reregistration Action
Risk Assessment Type: Single Chemical, Non-Food

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Attached is the Health Effect Division's preliminary risk assessment for the sulfometuron methyl RED. This risk assessment document was based on information contained in the following memos:

Occupational and Residential Exposure Assessment: W. Britton, D345025, 12/18/07
Water Memo: M. Barrett Ph.D., D334287, 10/31/07
DEEM Memo: W. Britton, D346139, 12/18/07
Incident Report: R. Allen Ph.D., M. Hawkins & H. Allender Ph.D., D343943

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1.0 Executive Summary

This assessment provides information to support the issuance of a risk management decision document known as a Reregistration Eligibility Decision (RED) Document for sulfometuron methyl. EPA's pesticide reregistration process provides for the review of older pesticides (those initially registered prior to November 1984) under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) to ensure that they meet current scientific and regulatory standards.

Sulfometuron methyl is a non-food/non-feed use chemical with no current or proposed usages which could lead to exposures from consuming raw agricultural commodities and/or processed foods. As a result, no tolerance levels have been established for this chemical and the requirements of the Food Quality Protection Act (FQPA) do not apply. Nevertheless, the present document considers all relevant exposure scenarios to sulfometuron methyl in order to provide an evaluation of the risks to human health arising from its supported uses. All drinking water and all but one occupational exposure scenarios evaluated were found to have risk levels below HED's level of concern.

Sulfometuron methyl is a nonselective, sulfonyl urea herbicide. It is labeled for commercial pre- and post-emergent applications to manage annual and perennial broadleaf weeds and grasses in non-agricultural sites (i.e., forestry, rights of way, non-crop industrial sites, and unimproved turf). Sulfometuron methyl acts by inhibiting acetolactate synthase (ALS), an enzyme that catalyzes the biosynthesis of three branched-chain amino acids (valine, leucine, and isoleucine), all of which are essential for plant growth. Control is generally for a full season or longer with only one required application per year; however, in some situations (i.e., weed escapes) a second application may be made, but the total applied annually should not exceed the maximum application rate.

According to the OPPIN Database, there are currently a total of 24 registered sulfometuron methyl products, of which 4 are technical or manufacturing concentrate formulations. All registered sulfometuron methyl products are formulated as water dispersable granules (WDGs), ranging from 18 to 75% ai. Applications range from 0.03 to 0.38 pound of active ingredient (ai) per acre and are directed via liquid spray using ground or aerial equipment. Based upon the 11/28/2006 sulfometuron methyl SMART meeting, there are no registered uses for sites which could be considered residential or recreational settings. While labeled use sites of sulfometuron methyl include turf (unimproved) and non-crop industrial, label language prohibits application to these sites in residential and recreational areas.

Hazard Characterization

Though the toxicological database for sulfometuron methyl is limited, it is considered to provide sufficient information to conduct a screening level risk assessment for the current use patterns. In order to refine the current risk estimates, additional toxicity studies would be required. In general, the data available indicate a low level of toxicity. The primary toxic effect of this sulfonyl urea pesticide is hemolytic anemia, which represents the most sensitive toxic endpoint for risk assessment. Sulfometuron methyl is not acutely toxic via the oral, dermal, or inhalation

routes of exposure. It shows minimal eye irritation and minimal skin irritation, but is not a dermal irritant or a dermal sensitizer.

A toxicity endpoint has been selected to assess potential risks resulting from drinking water and occupational exposure to sulfometuron methyl. An acute reference dose (aRfD), chronic reference dose (cRfD), and points of departure for dermal and inhalation toxicity were selected from a chronic dog feeding study. The endpoint for the acute reference dose selected from the chronic toxicity study provides a very conservative point of departure for acute risk assessment. In the absence of fully acceptable guideline studies which might yield a different acute endpoint (e.g., acceptable developmental toxicity studies), and considering the limited findings in the available developmental studies, use of the chronic dog endpoint will be protective.

The 21-day dermal rabbit study was determined to be insufficient to assess dermal exposures due to a number of deficiencies in the study. No route specific study was available for inhalation toxicity; therefore, an inhalation endpoint was selected based upon the chronic oral toxicity study. With chronic oral exposure, signs of hemolytic anemia were observed in dogs and body weight effects were seen beginning on the fourth week (and persisting throughout the entire study) of repeated exposure. Although no hematological or clinical chemistry assessments are available at the 4-week interval, the decreases in body weight gain noted beginning on the fourth week of the study provide an appropriate endpoint for short-term risk assessment. Since the hematological effects noted at the end of the study occurred at the same dose level as the body weight gain decrements seen beginning on the fourth week of exposure, this study and endpoints are also appropriate to assess potential intermediate- and long-term risks due to sulfometuron methyl exposure.

Carcinogenicity studies on sulfometuron methyl were not required since it is a non-food/non-feed pesticide and chronic exposure to this pesticide is not expected based on the use pattern. It was negative in the mutagenicity/genetic toxicity studies.

Dietary Exposure

Since sulfometuron methyl is a non-food/non-feed chemical, any potential dietary exposure arises from drinking water sources. It is mobile and persistent in the environment and it dissipates via aerobic and anaerobic degradation/ metabolism in soil and water (pseudo first-order degradation half-lives generally around 2 to 6 months), with hydrolysis potentially dominant under acidic conditions. Sulfometuron methyl's persistence in water indicates that if it reaches the surface water, it may persist for a few weeks to several months. The fairly low use rate and the apparent typical use pattern of applying in only one or two years out of a several year period should limit the actual exposure to sulfometuron methyl residues in surface water based drinking water, specifically over the chronic duration. While recognized as conservative, the potential exists for exposure from drinking water sources (surface and ground) and, therefore, an assessment was completed for acute and chronic exposure durations.

Conservative acute and chronic screening-level drinking water assessments were made with DEEM-FCID™, based upon the Environmental Fate and Effects Division's (EFED) determination of Estimated Drinking Water Concentrations (EDWCs) for exposure (M. Barrett,

D334287). The results indicate that exposures to sulfometuron methyl are below HED's level of concern. The analysis uses a survey-based consumption distribution together with an upper-bound residue value for drinking water. The acute and chronic drinking water exposure to sulfometuron methyl is estimated to be < 1 % of the RfDs for the general U.S. population. For the most highly exposed subgroup, all infants (< 1 year old), estimated acute dietary exposure is 2.3 % of the aRfD and chronic dietary exposure is < 1 % of the cRfD. Therefore, HED is not concerned that the non-food/non-feed use of sulfometuron methyl could result in unacceptable risk from potential exposure through drinking water sources.

Residential Handler and Postapplication Exposure/Risk

Residential exposure/risk (handler and postapplication) was not assessed since label instructions do not allow applications of sulfometuron methyl to residential or recreational settings.

Aggregate Risk

An aggregate exposure assessment, which combines exposures from different sources and routes, is typically conducted for non-food/ non-feed chemicals when there is potential for human exposure through water and residential pathways. Since sulfometuron methyl has no residential uses, the only source of exposure is from drinking water; therefore, an aggregate exposure assessment was not performed.

Occupational Handler Exposure/Risk

Sulfometuron methyl products are registered for use in the occupational environment to manage annual and perennial broadleaf weeds and grasses in a variety of sites (i.e., forestry, non-crop industrial, unimproved turf, and non-crop habitat restoration). As a result, occupational handlers of sulfometuron methyl could potentially be exposed during the application process.

Short- (up to 30 days) and intermediate-term (30 days to 6 months) dermal and inhalation exposure/risk was calculated for occupational handlers of sulfometuron methyl for different exposure scenarios. Long-term handler exposures (greater than 6 months) are not expected to occur. All but one of the occupational handler short- and intermediate-term scenarios assessed (dermal and inhalation combined) resulted in risk estimates (MOEs) ≥ 100 at some level of personal protection and, therefore, are not of concern. The exposure scenario mixing/loading WDGs for aerial application to forestry and non-crop areas results in a combined MOE = 90 at the maximum level of personal protection (double layer with gloves) and, therefore, is of potential concern. However, this concern is significantly reduced because of the use of conservative inputs in the risk estimates (e.g., 100% dermal absorption).

An occupational postapplication assessment of exposure to sulfometuron methyl was not performed. Since sulfometuron methyl is a non-selective herbicide used in non-agricultural areas, HED has determined that contact with previously treated areas is likely to be insignificant.

Environmental Justice Considerations

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.eh.doe.gov/oepa/guidance/justice/eo12898.pdf).

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas postapplication are evaluated. Further considerations are currently in development, as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

Review of Human Research

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 (listed in Appendix B) have been determined to require a review of their ethical conduct, have received that review and have been determined to be ethical.

Additional Data Needs

No additional data are needed to support the human health assessment of sulfometuron methyl.

2.0 Ingredient Profile

Sulfometuron methyl is a non-selective, sulfonyl urea herbicide labeled for commercial pre- and post-emergent applications to manage annual and perennial broadleaf weeds and grasses.

Summary of Use Patterns, Formulations and Application Methods

All sulfometuron methyl products are formulated as WDG (ranging from 18 to 75% ai) and are directed to the target via liquid spray applications via aerial or ground application methods. Registered uses of sulfometuron methyl include:

- forestry (conifers, hardwoods, hybrid poplar plantations);
- non-crop industrial sites (public, private, and military lands, rights-of-way, under asphalt and concrete);
- turf (unimproved); and
- non-crop habitat restoration sites.

Application Rates, Timing and Frequency of Applications

Application rates of sulfometuron methyl range from 0.03 to 0.38 pound of active ingredient (ai) per acre. Control is generally for a full season or longer with only one application per year; however, in some situations (i.e., weed escapes) a second application may be made, but the total applied annually should not exceed the maximum application rate.

Application Methods

Applications of sulfometuron methyl can be made aerially (helicopter and fixed-wing airplane) or by ground (high and low pressure handwand, groundboom, and rights-of-way sprayer). Low pressure handwand applications are typical for selective foliar applications (applied to target vegetation), while aerial, groundboom, and rights-of-way applications are specific to wide-area, broadcast treatments.

2.1 Structure and Nomenclature

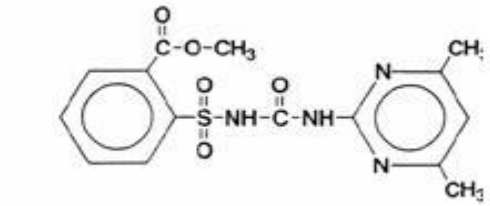
Table 2.1.a. Test Compound Nomenclature – Sulfometuron Methyl	
Chemical Structure	
Empirical Formula	$C_{15}H_{16}N_4O_5S$
Common Name	Sulfometuron Methyl
IUPAC name	methyl 2-(4,6-dimethylpyrimidin-2-ylcarbamoylsulfamoyl)benzoate
CAS Name	methyl 2-[[[[(4,6-dimethyl-2-pyrimidinyl)amino]carbonyl]amino]sulfonyl]benzoate
CAS Registry Number	74222-97-2
Chemical Class	Pyrimidinylsulfonylurea Herbicides

Table 2.1.b. Physiochemical Properties		
Parameter	**Value**	**Reference**
Molecular Weight	364.4	The Pesticide Manual: A World Compendium, 9th ed., 1991, C.R. Worthington, ed. The British Crop Protection Council, Surrey, UK pg. 774
Melting point	203-205°C	
Physical state	Colorless Solid	
Vapor pressure (25°C)	6.0×10^{-5} mm Hg	
Water solubility (25°C)	70 ppm	
Log Kow (25°C)	1.2	

3.0 Hazard Characterization/Assessment

The toxicology database for sulfometuron methyl is limited, but sufficient to provide screening level endpoints for this non-food/non-feed pesticide. Since risks are generally not of concern based on this screen, additional data will not be required at this time. However, if significant additional uses are requested, additional toxicity data will be required.

Sulfometuron methyl is not acutely toxic. The acute oral LD_{50} in rats is > 5 g/kg (Toxicity Category IV), the acute dermal LD_{50} is > 2 g/kg (Toxicity Category III), and the acute inhalation LC_{50} > 5.0 mg/L (Toxicity Category IV). Sulfometuron methyl shows minimal eye irritation and minimal skin irritation, but is not considered a dermal irritant or dermal sensitizer.

The primary toxic effect of this sulfonyl urea pesticide is hemolytic anemia (the most sensitive toxic endpoint) reported in the chronic oral toxicity study in dogs. This observation is consistent with reports in the open literature where hemolytic anemia has been identified as a side effect of sulfonyl urea compounds (e.g., chlorpropamide, LY186641) used therapeutically as anti-diabetic or anti-tumor agents[1]. In addition to hemolytic anemia, decreases in body weight were also seen in the chronic oral toxicity study beginning on the fourth week of exposure and persisting throughout the duration of the study.

Other studies available in the database include a dermal toxicity study as well as pre-natal developmental toxicity studies (in rats and rabbits). Due to a number of deficiencies identified in the conduct of these studies, they were not deemed suitable for endpoint selection in the risk assessment. Nonetheless, based on the information provided within these studies, the Agency is confident that the use of the chronic oral toxicity study in dogs would result in a health protective, albeit conservative, risk assessment. In the rabbit pre-natal developmental toxicity study, a slight increase in the incidence of abortions was observed from doses close to or at the limit dose (750 and 1000 mg/kg/day) while no evidence of toxicity *via* the dermal route was reported after 21 days of exposure at a dose 2-fold higher than the limit dose. Given the limited use pattern and low likelihood for chronic durations of exposure for this compound, no rodent chronic toxicity or carcinogenicity studies are required. It was negative in the mutagenicity/ genetic toxicity studies.

3.1 Hazard and Dose-Response Characterization

3.1.1 Database Summary

[1] J.A. Kopicky and C.H. Packman (1986) *The mechanisms of sulfonyul-urea induced immune hemolysis: Case report and review of the literature.* Amer. J. Hematol.. **23(3)**: 283-288
Ehlhardt, W.J., *et al.* (1997) *Disposition and metabolism of the sulfonyl urea oncolytic agent LY295501 in mouse, rat, and monkey.* Drug Met. Disp. **(25):6**: 701-712
Lee, C.W. et al. (2002). A novel stereo-selective sulfonylurea, 1-[1-(4-aminobenzoyl)-2,3-dihydro-1H-indol-6-sulfonyl]-4-phenylimidazolidin-2-one, has antitumor efficacy in in vitro and in vivo tumor models. Biochem. Pharmacol. **64(3):** 473-480

3.1.1.1 Sufficiency of studies/data

Sulfometuron methyl is registered as a non-food use chemical. The available toxicological data on sulfometuron methyl is limited, but sufficient to assess the potential hazard that may result from sulfometuron methyl exposure. The 21-day dermal and pre-natal developmental toxicity studies in rats and rabbits were classified as non-guideline due to multiple deficiencies and, therefore, were not used for risk assessment purposes. The following study was used to select toxicity endpoints and doses.

- Chronic Feeding – Dog: MRID No. 0129051

3.1.1.2 Mode of Action, Metabolism, Toxicokinetic Data

Studies demonstrating the mode of action of sulfometuron methyl in mammals have not been identified in the data base. In addition, no metabolism or kinetic studies were identified in the literature

3.2 Absorption, Distribution, Metabolism, Excretion (ADME)

No data were available for assessment.

3.3 Hazard Identification and Toxicity Endpoint Selection

The toxicity endpoints and doses for risk assessment were selected based upon the available toxicity data considering the use profile for sulfometuron methyl. The selected toxicity endpoints and doses are presented below.

3.3.1 Acute Reference Dose (aRfD) – All Population Subgroups

Study Selected: Chronic Feeding – Dog

MRID No.: 0129051

Executive Summary: See Appendix A, Guideline [§ 870.4100]

Dose and Endpoint for Risk Assessment: A NOAEL of 27.5 mg/kg/day and LOAEL of 148.5 mg/kg/day were selected to establish an aRfD based on hemolytic anemia in both sexes and decreased body-weight gain in males beginning on the fourth week of exposure (and persisting throughout the entire study).

Uncertainty Factor(s): 100X [10 interspecies; 10X intraspecies]

Comments about Study/Endpoint/Uncertainty Factors: Although sulfumeturon methyl is considered a non-food/non-feed chemical and no tolerances are associated with this registration, an aRfD was established for the purposes of conducting a drinking water risk assessment. Selection of the endpoint for the acute reference dose from a chronic toxicity study provides a

very conservative point of departure for acute risk assessment. In the absence of fully acceptable guideline studies which might yield a different acute endpoint (e.g., acceptable developmental toxicity studies) and considering the limited findings in the available developmental studies, use of the chronic dog endpoint will be protective.

3.3.2 Chronic Reference Dose (cRfD)

Study Selected: Chronic Feeding – Dog

MRID No.: 0129051

Executive Summary: See Appendix A, Guideline [§ 870.4100]

Dose and Endpoint for Risk Assessment: A NOAEL of 27.5 mg/kg/day and LOAEL of 148.5 mg/kg/day were selected to establish a cRfD based on hemolytic anemia in both sexes and decreased body-weight gain in males beginning on the fourth week of exposure (and persisting throughout the entire study).

Uncertainty Factor(s): 100X [10X interspecies; 10X intraspecies]

Comments about Study/Endpoint/Uncertainty Factors: The study duration and route of exposure are appropriate for this risk assessment. Moreover, a clear NOAEL for the effects of concern (hemolytic anemia, body weight parameters, and alkaline phosphatase) has been identified in the study.

3.3.3 Dermal Absorption

No dermal absorption data are available. As a result, a default 100% dermal absorption factor is assumed in this risk assessment.

3.3.4 Dermal Exposure (Short-, Intermediate- and Long-Term)

Study Selected: Chronic Feeding – Dog

MRID No.: 0129051

Executive Summary: See Appendix A, Guideline [§ 870.4100]

Dose and Endpoint for Risk Assessment: A NOAEL of 27.5 mg/kg/day and LOAEL of 148.5 mg/kg/day were selected to establish a cRfD based on hemolytic anemia in both sexes and decreased body-weight gain in males beginning on the fourth week of exposure (and persisting throughout the entire study).

Uncertainty Factor(s): 100X [10X interspecies; 10X intraspecies]

Comments about Study/Endpoint/Uncertainty Factors: No acceptable/guideline route-specific

studies are available for this risk assessment. As a result, the chronic toxicity study in dogs has been selected for risk assessment purposes. Although no hematological or clinical chemistry assessments are available at the 4-week interval, the decreases in body weight gain noted beginning on the fourth week of the study provide an appropriate endpoint for short-term risk assessment. Since the hematological effects noted at the end of the study occurred at the same dose level as the body weight gain decrements seen beginning on the fourth week of the study, this study and endpoints are also appropriate to assess potential intermediate- and long-term risks due to sulfometuron methyl exposure.

3.3.5 Inhalation Exposure (Short- and Intermediate -Term)

Study Selected: Chronic Feeding – Dog

MRID No.: 0129051

Executive Summary: See Appendix A, Guideline [§ 870.4100]

Dose and Endpoint for Risk Assessment: A NOAEL of 27.5 mg/kg/day and LOAEL of 148.5 mg/kg/day were selected based on hemolytic anemia in both sexes and decreased body weight gain in males beginning on the fourth week of the study (and persisting throughout the entire study).

Uncertainty Factor(s): 100X [10X interspecies; 10X intraspecies]

Comments about Study/Endpoint/Uncertainty Factors: With the exception of the acute inhalation toxicity study, no acceptable/guideline route-specific studies are available for this risk assessment. As a result, the chronic toxicity study in dogs has been selected for risk assessment purposes. Although no hematological or clinical chemistry assessments are available at the 4-week interval, the decreases in body weight gain noted beginning on the fourth week of the study provide an appropriate endpoint for short-term risk assessment. Since the hematological effects noted at the end of the study occurred at the same dose level as the body weight gain decrements seen beginning on the fourth week, this study and endpoints are also appropriate to assess potential intermediate- and long-term risks due to sulfometuron methyl exposure.

3.3.6 Level of Concern for Margin of Exposure

Table 3.3.6. Summary of 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		
Inhalation	NA	NA
Incidental Oral	NA	NA

A 100X uncertainty factor should be applied. The Uncertainty Factor accounts for both interspecies extrapolation (10X) and intraspecies variability (10X).

3.3.7 Classification of Carcinogenic Potential

There are no carcinogenicity studies for sulfometuron methyl since it is a non-food/non-feed pesticide and chronic exposure to this pesticide is unlikely. It was negative in the available mutagenicity/genetic toxicity studies.

3.3.8 Summary of Toxicological Doses and Endpoints for Sulfometuron Methyl

Table 3.3.8. Summary of Toxicological Doses and Endpoints for Sulfometuron Methyl for Use in Dietary and Non-Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty Factors**	**RfD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary (all population subgroups)	NOAEL= 27.5 mg/kg/day	UF_A= 10 x UF_H=10 x	Acute RfD = 0.275 mg/kg/day	Chronic 1-year dog study LOAEL = 148.5 mg/kg/day based on decreases in body weight in males (beginning on the fourth week of exposure and persisted throughout), hemolytic anemia and a slight increase in alkaline phosphatase in males and females.
Chronic Dietary (All Populations)			Chronic RfD = 0.275 mg/kg/day	
Dermal Short- (1-30 days) and Intermediate-Term (1-6 months) (no residential uses)	NOAEL= 27.5 mg/kg/day	UF_A= 10x UF_H= 10x	LOC for MOE = 100	
Inhalation Short- (1-30 days) and Intermediate-Term (1-6 months) (no residential uses)				
Cancer (oral, dermal, inhalation)	No data available for assessment.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

3.4 Endocrine Disruption

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

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

4.0 Public Health and Pesticide Epidemiology Data

Incident report was incomplete at the time of document submission.

[See R.H. Allen, M. Hawkins & H. Allender, D343943]

5.0 Dietary Exposure/Risk Characterization

The only potential dietary exposures to sulfometuron methyl would be from drinking water sources since this is a non-food/non-feed chemical.

5.1 Pesticide Metabolism and Environmental Degradation

[See M. Barrett, D334287, 10/31/2007]

The body of environmental fate data submitted demonstrates sulfometuron methyl is mobile and persistent in the environment. It is more soluble in neutral and alkaline water than in acidic water. The major route of dissipation for sulfometuron methyl is believed to be aerobic and anaerobic degradation/ metabolism in soil and water (pseudo first-order degradation half-lives generally around 2 to 6 months), with hydrolysis potentially dominant under acidic conditions.

Estimated drinking water concentrations (EDWCs) were formulated for surface and ground water for total residues including the parent compound, sulfometuron methyl, as well as the potential water degradates sulfometuron free acid, sulfometuron pyrimidine amine, sulfometuron sulfonamide, and saccharin.

Drinking Water Exposure Estimation

While some monitoring data are available, the data are not targeted to watersheds known to present the highest exposure potential for sulfometuron methyl. Consequently, EFED's Tier I models were used for this drinking water exposure assessment.

Surface Water Modeling

The FIRST (FQPA Index Reservoir Screening Tool, Version 1.1.0) model by the Environmental Fate and Effects Division (EFED) of the USEPA Office of Pesticide Programs (OPP) was used to assess potential for contamination of surface drinking water sources from the proposed sulfometuron methyl use.

FIRST is a single-event model (one runoff event), but can account for spray drift from multiple applications. FIRST is hardwired to represent the Index Reservoir, a standard water body used by the Office of Pesticide Programs to assess drinking water exposure (Office of Pesticide Programs, 2002). It was based on a real reservoir, Shipman City Lake in Illinois, which was known to be vulnerable to pesticide contamination (with ample confirmation from pesticide monitoring data). The single runoff event moves a maximum of 8% of the applied pesticide into the reservoir. This amount can be reduced due to degradation on the field and the effects of binding to soil in the field. FIRST also uses a Percent Cropped Area (PCA) factor to adjust for the area within the watershed that is planted to the modeled crop. The national default PCA of 0.87 (i.e., 87 %) was applied in this assessment.

Ground Modeling

Sulfometuron methyl concentrations in ground water were estimated by the Screening Concentration in Ground Water (SCI-GROW v2.3, Jul. 29, 2003) model. SCI-GROW is a regression model used as a screening tool to estimate pesticide concentrations found in groundwater used as drinking water. SCI-GROW was developed by fitting a linear model to ground water concentrations with the Relative Index of Leaching Potential (RILP) as the independent variable. Groundwater concentrations were taken from 90-day average high concentrations from Prospective Ground Water studies. The RILP is a function of aerobic soil metabolism and the soil-water partition coefficient. The output of SCI-GROW represents the concentrations of sulfometuron methyl residues that might be expected in shallow unconfined aquifers under sandy soils.

Further information on these models can be found at the EFED water model website at http://www.epa.gov/oppefed1/models/water/html.

Model Inputs and Results (Drinking Water Estimated Concentrations)

For a complete description of model inputs and results please reference the following: M. Barrett, D334287, 10/31/2007. Table 5.1 presents the EDWCs of total residues (i.e., parent compound and degradates) in drinking water from surface and ground water sources as resulting from EFED water modeling. Given the limited environmental fate data on the degradates, no estimation of individual degradate concentrations is possible at this time. The EDWCs cannot be manipulated to provide separate degradate and parent compound values.

Table 5.1. Tier I EDWCs for Sulfometuron Total Residues from Forestry or Rights of Way Uses*

Chemical	Application			Peak Day (Acute)	Annual Average (Chronic)
Surface Water	**Rate (lb a.i./A)**	**Number**	**Interval (days)**	**Concentration (µg/L)**	
Aerial	0.375	1	NA	**32.35**	**21.82**
Aerial	0.188	2	30	30.21	20.38
Ground Water					
Aerial or ground	0.375	1	NA	1.13	1.13

* Includes sulfometuron methyl, sulfometuron free acid, sulfometuron pyrimidine amine, sulfometuron sulfonamide, and saccharin

5.2 Dietary Exposure Estimates

[See W. Britton, D346139, 12/18/07]

An unrefined acute and chronic screening-level drinking water only dietary assessment was conducted for the herbicide sulfometuron methyl using the Dietary Exposure Evaluation Model DEEM-FCID™, Version 2.03 which use food consumption data from the U.S. Department of Agriculture's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998 to calculate dietary risk. Sulfometuron methyl is a non-food/non-feed use chemical with no current or proposed usages which could lead to dietary exposures from raw agricultural commodities and/or processed foods. Consequently, sulfometuron methyl dietary risk was assessed based on drinking water exposures only. Also, FQPA requirements are not applicable to the current action pursuant to this RED, therefore, the screening level risk estimates are expressed as RfDs rather than population adjusted doses (PADs).

The drinking water concentrations used in the dietary risk assessment were provided by the Environmental Fate and Effects Division (EFED) in the following memorandum: "Tier I Sulfometuron Methyl Drinking Water Assessment for Reregistration Eligibility Decision Document" (M. Barrett, D334287, 10/31/07) and incorporated directly, as single point estimates, into this dietary assessment. This unrefined assessment relied solely on modeling analyses to calculate both surface and ground water EDWCs for exposure. A number of degradates were identified and these have been added to the parent compound sulfometuron methyl. The drinking water assessment, therefore, models the parent compound sulfometuron methyl as well

as the potential water degradates sulfometuron free acid, sulfometuron pyrimidine amine, sulfometuron sulfonamide, and saccharin, as the combined residues of parent and metabolites. It is conservative in its approach and is unlikely to underestimate the concentration of sulfometuron methyl in drinking water. The highest ground and surface water (acute) EDWCs relevant to the maximum supported use rate of sulfometuron methyl were 1.1 and 32.4 ppb, respectively. The highest ground and surface water (chronic) EDWCs relevant to the maximum supported use rate of sulfometuron methyl were 1.1 and 21.8 ppb, respectively. Accordingly, the larger values of 32.4 (acute) and 21.8 (chronic) ppb were used in the present acute and chronic screening-level drinking water dietary assessments. Again, food uses were not incorporated into this evaluation since only non-food/non-feed uses of sulfometuron methyl are being supported by the registrant.

Results for Acute Dietary Exposure Analysis

An acute dietary risk analysis was conducted with the DEEM-FCID™ model to form a conservative evaluation of exposure for sulfometuron methyl. The acute analysis yielded estimates well below the 100% of the aRfD threshold exposure level of concern for the US population and each population subgroup. For the US Population, acute dietary risk was calculated at < 1 % of the aRfD with an exposure level of 0.0017 mg/kg/day. For the subgroup with the highest esimated exposure, all infants less than 1 year old, acute dietary risk occupied 2.3 % of the aRfD with an exposure of 0.0064 mg/kg/day. An overview summarizing the results of the acute dietary assessment with the population subgroup having the highest exposure being noted in bold is presented in Table 5.2.1.

Table 5.2.1. Summary of Screening Level Drinking Water Exposure and Risk for Sulfometuron Methyl

Population Subgroup	Acute Dietary[1]	
	Dietary Exposure (95th percentile) (mg/kg/day)	%aRfD
General U.S. Population	0.001690	< 1
All Infants (< 1 year old)	**0.006372**	**2.3**
Children 1-2 years old	0.002652	< 1
Children 3-5 years old	0.002422	< 1
Children 6-12 years old	0.001686	< 1
Youth 13-19 years old	0.001371	< 1
Adults 20-49 years old	0.001566	< 1
Adults 50+ years old	0.001414	< 1
Females 13-49 years old	0.001575	< 1

[1] Acute dietary analysis based on a 0.275 mg/kg/day aRfD.

Results of Chronic Dietary Exposure Analysis

A chronic dietary risk analysis was conducted with the DEEM-FCID™ model to form a conservative evaluation of exposure for sulfometuron methyl. The chronic analysis yielded risk estimates well below the 100% of the cRfD threshold level of concern for the US population and each population subgroup. For the US population, chronic dietary risk was calculated at < 1 % of the cRfD with an exposure level of 0.00046 mg/kg/day. For the subgroup with the highest estimated exposure, all infants less than 1 year old, chronic dietary risk occupied < 1 % of the cRfD with an exposure of 0.0015 mg/kg/day. An overview summarizing the results of the chronic dietary assessment with the population subgroup having the highest exposure being noted in bold is presented in Table 5.2.2.

Table 5.2.2. Summary of Screening Level Drinking Water Exposure and Risk for Sulfometuron Methyl

Population Subgroup	Chronic Dietary[1]	
	Dietary Exposure (99th percentile) (mg/kg/day)	%cRfD
General U.S. Population	0.000460	< 1
All Infants (< 1 year old)	**0.001508**	**< 1**
Children 1-2 years old	0.000683	< 1
Children 3-5 years old	0.000639	< 1
Children 6-12 years old	0.000441	< 1
Youth 13-19 years old	0.000332	< 1
Adults 20-49 years old	0.000429	< 1
Adults 50+ years old	0.000452	< 1
Females 13-49 years old	0.000428	< 1

[1] Chronic dietary analysis based on a 0.275 mg/kg/day cRfD.

Summary

The conservative acute and chronic screening-level drinking water dietary assessment made with DEEM-FCID™ indicates that exposures to sulfometuron are below HED's level of concern for the US population and all population subgroups. Therefore, HED is not concerned that the non-food/ non-feed use of sulfometuron methyl could result in unacceptable risk through potential exposure from drinking water sources.

6.0 Residential (Non-Occupational) Exposure/Risk

[See W. Britton, D345025, 12/18/07]

Residential exposure/risk (handler and postapplication) was not assessed since label instructions prohibit applications of sulfometuron methyl to residential or recreational settings.

6.1 Other (Spray Drift, etc.)

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 methods employed for sulfometuron methyl. 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.

7.0 Aggregate Risk Assessments and Risk Characterization

An aggregate exposure assessment is typically conducted for non-food chemicals when there is potential for human exposure through water and residential pathways. Since sulfometuron methyl has no residential uses, an aggregate exposure assessment was not performed.

8.0 Occupational Exposure/Risk Pathway

[See W. Britton, D345025, 12/18/07]

It has been determined there is a potential for exposure in occupational settings from handling sulfometuron methyl products during the application process (i.e., mixer/loaders, applicators, flaggers, and mixer/loader/applicators). A risk assessment has been completed for the occupational handling of sulfometuron methyl; however, an occupational postapplication assessment of exposure to sulfometuron methyl was not performed. Since sulfometuron methyl is a non-selective herbicide used in non-agricultural areas, contact with previously treated areas is likely to be insignificant.

Sulfometuron methyl is labeled for commercial pre- and post-emergent applications to manage annual and perennial broadleaf weeds and grasses. Application rates of sulfometuron methyl range from 0.03 to 0.38 pound of active ingredient (ai) per acre. All sulfometuron methyl products are formulated as WDG (ranging from 18 to 75% ai) and are directed to the target via liquid sprays applications via aerial or ground application methods. Applications of

sulfometuron methyl can be made aerially (helicopter and fixed-wing airplane) or by ground (high and low pressure handwand, groundboom, and rights-of-way sprayer). Registered uses of sulfometuron methyl include:

- forestry (conifers, hardwoods, hybrid poplar plantations);
- non-crop industrial sites (public, private, and military lands, rights-of-way, under asphalt and concrete);
- turf (unimproved); and
- non-crop habitat restoration sites.

Based upon the use pattern of sulfometuron methyl, HED anticipates both short- and intermediate-term occupational exposure. Long-term handler exposures are not expected to occur. The endpoint selected for dermal and inhalation exposure is for short- and intermediate-term durations. Risk estimates resulting from the assessment of dermal and inhalation exposure were combined since it is logical that these routes of exposure could co-occur.

8.1 Sulfometuron Methyl Occupational Handler Exposure Scenarios

Exposure to pesticide handlers is likely during the occupational use of sulfometuron methyl based on the types of equipment and techniques that can potentially be used. The quantitative exposure/risk assessment developed for occupational handlers is based on the following scenarios. Sulfometuron methyl exposure was estimated (combined dermal and inhalation) using the Pesticide Handlers Exposure Database (PHED) data. Mixer/loader exposure scenarios were estimated using PHED data specific to dry flowable (DF) products since this formulation is most similar to WDGs; however, all other tasks (i.e., applicators, flaggers, and mixer/loader/applicators) were assessed with PHED data specific to liquid products since the WDGs are mixed into and applied as a liquid.

Mixer/Loaders:
(1) WDG: Aerial (Fixed Wing Airplane and Helicopter)
(2) WDG: Groundboom
(3) WDG: Right-of-Way Applications

Applicators:
(4) Liquid: Aerial Applications (Fixed Wing Airplane and Helicopter)
(5) Liquid: Groundboom Applications
(6) Liquid: Rights of Way Applications

Flaggers:
(7) Flagging for Aerial Sprays

Mixer/Loader/Applicators:
(8) Liquid: Low Pressure Handwand Sprayer

8.1.1 Data and Assumptions for Handler Exposure Scenarios

Assumptions for Handler Exposure Scenarios

A series of assumptions and exposure factors served as the basis for completing the occupational handler risk assessments. The assumptions and factors used in the risk calculations include:

- HED has patterned this risk assessment on a series of likely representative scenarios that are believed by HED to represent the vast majority of sulfometuron methyl uses;

- Average body weight of an adult handler is 70 kg because the toxicity endpoint values used for the assessments are appropriate for average adult body weight representing the general population;

- For non-cancer assessments, HED assumes the maximum application rates allowed by labels in its risk assessments;

- Since no dermal absorption data are available, a default 100% absorption factor is assumed;

- The average occupational workday is assumed to be 8 hours; and

- The daily areas treated were defined for each handler scenario (in appropriate units) by determining the amount that can be reasonably treated in a single day (e.g. acres, square feet, or gallons per day). The assumptions for daily areas treated are taken from the HED ExpoSAC SOP #9: Standard Values for Daily Acres Treated in Agriculture which was completed on July 5, 2000.

    - Aerial Applications for Forestry – 1200 acres
    - Groundboom Applications – 200 acres
    - Flaggers – 350 acres
    - Right-of-Way Sprayer – 25 acres (based upon 1000 gallons/day, as specified by SOP #9, and a labeled rate of 40 gallons/acre)
    - Low Pressure Handwand Sprayer – 1 acre (based upon 40 gallons/day, as specified by SOP #9, and a labeled rate of 40 gallons/acre)

Data for Handler Exposure Scenarios

No chemical specific information was available for sulfometuron methyl handler exposure assessments. All occupational handler exposure estimates were completed using surrogate data from PHED. This data is outlined in Appendix A in the following document: W. Britton, D345025, 12/18/07.

8.1.2 Occupational Handler Exposure/Risk Estimates

Short- and intermediate-term dermal and inhalation exposures/risks were calculated for occupational handlers of sulfometuron methyl for different exposure scenarios. Most of the handler short- and intermediate-term scenarios assessed (dermal and inhalation combined) resulted in risk estimates (MOEs) ≥ 100 at some level of personal protection and, therefore, are not of concern. The exposure scenario mixing/loading of WDGs for aerial application to forestry and non-crop areas results in a combined MOE = 90 at the maximum level of personal protection (double layer with gloves) and, therefore, is of potential concern. A summary of risk calculations performed for occupational sulfometuron methyl handlers at baseline PPE is presented below in Table 8.1.2a; a summary of calculations for occupational sulfometuron methyl handlers with additional PPE is presented in Table 8.1.2b.

Table 8.1.2a. Sulfometuron Methyl MOEs Attributable to Short- and Intermediate-term Combined Dermal and Inhalation Occupational Exposure (Baseline PPE)[a]

No.	Scenario	Target	App. Rate[b] (lb ai/acre)	Area Treated (acres)	Dermal[c] MOEs	Inhalation[d] MOEs	Combined[e] MOEs
Mixer/Loaders							
1	WDGs: Aerial Equipment (Fixed Wing and Helicopter)	Forestry (Hardwoods, Conifers), Non-Crop Areas (Public, Private, Military Lands)	0.38	1200	65	5600	**64**
		Turf (Unimproved)	0.19		130	11000	130
		Non-Crop Land Restoration	0.09		260	22000	260
2	WDGs: Groundboom Equipment	Forestry (Hardwoods, Conifers), Non-Crop Areas	0.38	200	390	33000	380
		Turf (Unimproved)	0.19		780	66000	770
		Non-Crop Land Restoration	0.09		1500	130000	1500
3	WDGs: Rights-of-Way Equipment	Rights-of-Way, Non-Crop Areas	0.38	25	3100	270000	3100
		Turf (Unimproved)	0.19		6200	530000	6100
		Non-Crop Land Restoration	0.09		12000	1100000	12000
Applicators							
4	Liquids: Aerial Applications (Fixed Wing and Helicopter)	Forestry (Hardwoods, Conifers), Non-Crop Areas	0.38	1200	900	63000	840
		Turf (Unimproved)	0.19		1700	130000	1700
		Non-Crop Land Restoration	0.09		3400	250000	3400
5	Liquids: Groundboom Applications	Forestry (Hardwoods, Conifers), Non-Crop Areas	0.38	200	1800	35000	1700

Table 8.1.2a. Sulfometuron Methyl MOEs Attributable to Short- and Intermediate-term Combined Dermal and Inhalation Occupational Exposure (Baseline PPE)[a]							
No.	**Scenario**	**Target**	**App. Rate[b] (lb ai/acre)**	**Area Treated (acres)**	**Dermal[c] MOEs**	**Inhalation[d] MOEs**	**Combined[e] MOEs**
		Turf (Unimproved)	0.19		3700	70000	3500
		Non-Crop Land Restoration	0.09		7300	140000	7000
6	Liquids: Rights-of-Way Applications	Rights-of-Way, Non-Crop Areas	0.38	25	160	53000	160
		Turf (Unimproved)	0.19		320	110000	310
		Non-Crop Land Restoration	0.09		630	210000	630
Flaggers							
7	Liquids: Aerial Sprays (Fixed Wing and Helicopter)	Forestry (Hardwoods, Conifers), Non-Crop Areas	0.38	350	1300	42000	1300
		Turf (Unimproved)	0.19		2700	84000	2600
		Non-Crop Land Restoration	0.09		5300	170000	5200
Mixer/Loader/Applicators							
8	Liquids: Low Pressure Handwand	Non-Crop Areas	0.38	1	51	170000	**51**
		Turf (Unimproved)	0.19		100	340000	100
		Non-Crop Land Restoration	0.09		210	680000	210

a Baseline = Long pants, long-sleeved shirt, no gloves
b Application rate based upon maximum labeled value.
c Dermal MOE = Dermal NOAEL (27.5 mg/kg/day)/ (Dermal Daily Dose [Reference W.Britton, 345025])
d Inhalation MOE = Inhalation NOAEL (27.5 mg/kg/day) / (Inhalation Daily Dose [Reference W.Britton, 345025])
e Combined MOE = 1/((1/Dermal MOE)+(1/Inhalation MOE))

Table 8.1.2b. Sulfometuron Methyl MOEs Attributable to Short- and Intermediate-term Combined Dermal and Inhalation Occupational Exposure (Required Additional PPE)[a]							
No.	**Scenario**	**Target**	**App. Rate[a] (lb ai/acre)**	**Area Treated (acres)**	**Dermal[b] MOEs**	**Inhalation[c] MOEs**	**Combined[d] MOEs**
Mixer/Loaders - Double Layer with Gloves Level of PPE							
1	WDGs: Aerial Equipment (Fixed Wing and Helicopter)	Forestry (Hardwoods, Conifers), Non-Crop Areas (Public, Private, Military Lands)	0.38	1200	91	5600	90
Mixer/Loader/Applicators - Single Layer with Gloves Level of PPE							
8	Liquids: Low Pressure Handwand	Non-Crop Areas	0.38	1	12000	170000	12000

a Application rate based upon maximum labeled value.
b Dermal MOE = Dermal NOAEL (27.5 mg/kg/day)/ (Dermal Daily Dose [Reference W.Britton, 345025])
c Inhalation MOE = Inhalation NOAEL (27.5 mg/kg/day) / (Inhalation Daily Dose [Reference W.Britton, 345025])
d Combined MOE = 1/((1/Dermal MOE)+(1/Inhalation MOE))

8.1.3 Risk Characterization

The occupational handler dermal exposure scenario is the only scenario for which significant risks were estimated for some uses; other risk assessments completed (e.g., chronic and acute drinking water) were not of concern. Due to a number of deficiencies identified in the conduct of the 21-day dermal study, it was deemed unsuitable for endpoint selection. In lieu of a route-specific study, the endpoint from the chronic oral toxicity study in dogs was used to estimate the potential for risk from dermal exposure to sulfometuron methyl. The Agency is confident that the use of the chronic oral study results in a health protective risk assessment for the following reasons:

- Although the 21-day dermal study had significant flaws, no toxicity was observed at 2000 mg/kg/day following 21 days of dosing;

- The results of the acute dermal toxicity study in rabbits shows an $LD_{50} \geq 2000$ mg/kg [Toxicity Category III]); and

- Dermal risks, which drive handler risks, were calculated assuming 100% dermal absorption due to lack of acceptable dermal absorption data. Assuming even a slightly lower dermal absorption of 90%, which is still likely to exceed the actual dermal absorption, would result in risk estimates which are not of concern for all scenarios, assuming some level of personal protective equipment is employed.

The exposure scenario mixing/loading of WDGs for aerial application to forestry and non-crop areas results in the lowest combined MOE = 90 at the maximum level of personal protection (double layer with gloves). While this exposure scenario is of potential concern, this concern is significantly reduced because of the use of the conservative inputs described above.

8.2 Occupational Postapplication Exposures and Risks

HED uses the term "postapplication" to describe exposures to individuals that occur as a result of being in an environment that has been previously treated with a pesticide (also referred to as reentry exposure). HED believes that there are distinct job functions or tasks related to the kinds of activities that occur in previously treated areas. Job requirements (e.g., the kinds of jobs to cultivate a crop), the nature of the crop or target that was treated and how the chemical residues degrade in the environment can cause exposure levels to differ over time.

An assessment of occupational postapplication exposure to sulfometuron methyl was not performed. Since sulfometuron methyl is a non-selective herbicide used in non-agricultural areas, HED has determined that contact with previously treated areas is likely to be insignificant.

9.0 Data Needs and Label Recommendations

No additional data are required.

Appendix A: Toxicology Assessment

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.340) for a non food/feed use for sulfometuron methyl are in Table 1. 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	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes[1]	yes[2]
870.3150	Oral Subchronic (nonrodent)[1]	yes[1]	-
870.3200	21-Day Dermal	yes[1]	no
870.3250	90-Day Dermal	no	-
870.3465	90-Day Inhalation	no	-
870.3700a	Developmental Toxicity (rodent)	yes	no
870.3700b	Developmental Toxicity (nonrodent)	yes	no
870.3800	Reproduction	no	-
870.4100a	Chronic Toxicity (rodent)	no	no
870.4100b	Chronic Toxicity (nonrodent)	no	yes
870.4200a	Oncogenicity (rat)	no	no
870.4200b	Oncogenicity (mouse)	no	no
870.4300	Chronic/Oncogenicity	no	no
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)	no	-
870.6200b	90-Day Neuro. Screening Battery (rat)	no	-
870.6300	Develop. Neuro	no	-
870.7485	General Metabolism	no	-
870.7600	Dermal Penetration	no	no
Special Studies for Ocular Effects			
	Acute Oral (rat)	no	-
	Subchronic Oral (rat)	no	-
	Six-month Oral (dog)	no	-

[1] Conditionally required
[2] Chronic dog study satisfies requirement for a subchronic toxicity study in the rodent

A.2 Toxicity Profiles

Table A.2.1 Acute Toxicity Profile - Test Substance[1]

Guideline No.	Study Type	MRID No.(s)	Results	Toxicity Category
870.1100	Acute oral rat	43089201	LD_{50} >5g/kg	IV
870.1200	Acute dermal rabbit	43089202	LD_{50} >2g/kg	III
870.1300	Acute inhalation rat	43089203	LC_{50} >5.0 mg/L	IV
870.2400	Acute eye irritation rabbit	00071412	Minimal irritant	III
870.2500	Acute dermal irritation rabbit	41672808	Not a dermal irritant*	IV
870.2600	Skin sensitization rabbit	43089204	Not a dermal sensitizer	N/A

[1] All studies were conducted on technical grade Sulfometuron methyl, of at least 98.8%, purity.
* Minimal skin irritation was noted in the acute dermal toxicity study (MRID No. 43089202) and an older dermal irritation study of a 75% formulation (MRID No. 00071411)

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3200	21-Day dermal toxicity (rabbit)	00126714 (1983) Acceptable/non-guideline M/F: 0, 125, 500, 2000 mg/kg/day	NOAEL = 2000 mg/kg/day LOAEL = Not observed
870.3700a	Prenatal developmental (rabbit)	00078798 (1981) Acceptable/non-guideline F:0, 30, 100, 300 mg/kg/day	**Maternal** NOAEL =300 mg/kg/day (HDT) LOAEL = 750 mg/kg/day based on abortion observed in the range-finding study. **Developmental** NOAEL =300 mg/kg/day LOAEL not observed
	Prenatal developmental (rabbit) – Range-finding study	00078797 (1981) F: 100, 300, 750, 1000 mg/kg/day	**Maternal** LOAEL = 750 mg/kg/day based on abortion
870.3700b	Prenatal developmental in (rat)	00078796 (1981) Unacceptable/guideline Run I F: 0, 5,000, 20,000, 40,000 and 60,000 ppm Run II & III F: 0, 50, 1000 and 5,000 ppm (433 mg/kg/day)	**Maternal** NOAEL> 433 mg/kg/day LOAEL not observed **Developmental** NOAEL>433 mg/kg/day LOAEL not observed
870.4100b	Chronic toxicity (dog)	00129051 (1983) Acceptable/guideline M: 0, 5.2, 27.5, 152.6 mg/kg/day F: 0, 5.3, 28.3, and 148.5 mg/kg/day	NOAEL = 27.5mg/kg/day LOAEL = 148.5 mg/kg/day, based on hemolytic anemia in both sexes, decreased body-weight gain in males, and increased alkaline phosphatase in males and females. Effects on body weight were observed beginning on the fourth week of exposure (and persisting throughout the study).
Gene Mutation	Salmonella/ Microsome assay	00078792 (1979) Acceptable/guideline in strains TA 1535, TA 1537, TA 98 and TA 100 in the presence or absence of activation.	No mutagenic activity for all strains of bacteria tested.
Gene mutation	Chinese Hamster Ovary	00078793 (1981) Acceptable/guideline CHO cell line was used to detect mutations for HGPRT	No mutagenic activity with or without activation.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
Chromo-some aberration	Chinese Hamster Ovary in vitro cytogenetic assay	00146846 (1981) Acceptable/guideline CHO in vitro assay with and without activation	No increase in chromosome damage and aberrations.
Un-scheduled DNA synthesis	Unscheduled DNA synthesis in rat hepatocytes *in vitro*	00146847 (1983) Acceptable/guideline	No induction of UDS was observed.

A.3 Executive Summaries

A.3.1 870.3200 21-Day Dermal Toxicity – Rabbit

In a repeated-dose dermal toxicity study (MRID No. 00126714), sulfometuron-methyl (purity and batch/lot # were not reported) was applied as an aqueous paste to the shaved intact skin (surface area treated not reported) of 5 New Zealand White rabbits/sex/dose at dose levels of 0, 125, 500, or 2000 mg/kg/day, 6 hours/day for 21 consecutive days. At the conclusion of the treatment period, 3 rabbits/sex/dose were sacrificed and subjected to gross and microscopic pathological evaluations. The remaining 2 rabbits/sex/dose were allowed to recover for 14 days, after which the animals were sacrificed and subjected to gross and microscopic pathological evaluations.

No adverse compound-related effects were observed in mortality, clinical signs of toxicity, body weight, hematology, clinical chemistry, or gross or microscopic pathology in either sex.

The LOAEL was not observed. The NOAEL is 2000 mg/kg/day (2x the limit dose).

The study is classified as acceptable/non-guideline and it does not satisfy the guideline requirement for a 21-day dermal toxicity study (OPPTS 870.3200; OECD 410) in rabbits. The study is considered non-guideline due to a number of deficiencies which include: test animals utilized were diseased, daily observation and dermal irritation data were absent, no animal husbandry data were available, no organ weight data were provided, no purity lot/batch or stability data were submitted, no compliance statements were presented. In addition, too few animals per group were tested to meet guideline requirements.

A.3.2 Prenatal Developmental Toxicity

870.3700a Prenatal Developmental Toxicity Study - Rat

In a developmental toxicity study (MRID No. 00078796) sulfometuron methyl (98.8%; Batch # 13647-02) was initially fed to 10, 10, 11, 13 and 2 Sprague Dawley rats/group at dietary concentrations of 0, 5000, 20,000, 40,000, or 60,000 ppm, respectively, from gestation days 6-15 (identified in the study as Run I). Subsequently, the doses were reduced and the study repeated, in two additional runs (II and III) with combined totals of 35 (plus the 10 animals from Run I), 25, 23, and 15 rats (plus the two animals from Run I) per group at dietary dose levels of 0, 50, 1000, or 5000 ppm, respectively, from gestation days (GD) 6-15. On GD 21, all dams were euthanized, and the uterus was removed via cesarean section and its contents examined. Fetuses were examined for external, visceral, and skeletal malformations and variations. The applicable data from study runs I, II and III were combined although these studies were not concurrent. No rationale for dietary administration was provided.

There were no mortalities and no treatment-related clinical signs or macroscopic findings. During the treatment interval, decreases ($p \leq 0.05$) in maternal body weight gain (decr. 11%) and food consumption (decr. 4%) were observed at 5000 ppm compared to controls. The small change in weight gain is minimal (represents only 6.4 grams in a 300 gram animal, or a change

of just 2% in body weight) and appears to be associated with reduced food consumption at the high dose. Therefore, the effect might be associated with diet palatability rather than toxicity in consideration of the high concentration in diet during Runs II and III (5000 ppm) and up to 60,000 ppm in Run I. In addition, the corrected body weights and body weight gains at day 21 are not affected suggesting further that there is no significant overt maternal toxicity at any dose level in this study. During the post-treatment interval, body weights and body weight gains in this group were comparable to controls. However, no individual animal data were available to confirm this assessment.

A maternal LOAEL was not observed at 5000 ppm (equivalent to 433 mg/kg/day), the highest dose tested (HDT).

There were no abortions, premature deliveries, or complete litter resorptions. Furthermore, there were no effects of treatment on numbers of litters, live fetuses, deaths/resorptions, or on post-implantation loss. However, no individual animal data were available in the submitted report to confirm this assessment.

Fetal body weights were decreased ($p \leq 0.05$) by 5% at 5000 ppm. This finding might be associated with the reduced food consumption observed in dams at this dose level which appears to have contributed to a slight reduction in their mean body weights (however, no individual food consumption or body weight data were available in the submitted report to assess or confirm these findings) and therefore the effect observed at the high dose level (5000 ppm) could be associated with slightly reduced dietary consumption and body weight of the dams. Also note that one reported concern of the investigators was palatability at such a high dietary dose and typically dietary developmental toxicity studies are avoided in the assessment of developmental toxicity for similar and other reasons which complicate interpretation of maternal and developmental toxicity. Thus, fetal weight reductions observed might be associated with reduced dietary consumption of dams with associated maternal effects (slightly lower body weights) and might not reflect actual fetal toxicity. Further, this effect represents only a 0.2 gram difference in mean fetal weights as compared to controls and only a 0.1 gram difference as compared to mean fetal weights at the low dose level, a dose $1/100^{th}$ of the high dose level. In addition, mean litter size was also greatest at the high dose level which also might result in slightly smaller fetal weights at that level. No individual animal data were provided in the report to support the summary data assessment.

There were no treatment-related external, visceral, or skeletal malformations or variations. However, no individual litter data were provided in the test report.

A developmental LOAEL was not observed in this dietary developmental toxicity study at 5000 ppm (equivalent to 433 mg/kg/day).

This study is classified as **unacceptable/guideline** and it does not satisfy the guideline requirement for a developmental toxicity study in rats (OPPTS 870.3700; OECD 414). Overt maternal toxicity was not demonstrated in this dietary study. In addition, while under certain circumstances dietary developmental studies may be considered as acceptable, no rationale/justification was included in the report to support administration via this route.

870.3700b Prenatal Developmental Toxicity Study – Rabbit

In a developmental toxicity study (MRID No. 00078798) Sulfometuron-methyl (100% a.i.; Batch # not provided) in 0.5% aqueous methylcellulose was administered via oral gavage at a dose volume of 4 mL/kg to 17 artificially inseminated New Zealand White rabbits/dose group at doses of 0, 30, 100, or 300 mg/kg/day from gestation days (GD) 6-18. On GD 29, all does were euthanized, and the uterus was removed via cesarean section and its contents examined. Fetuses were examined for external, visceral, and skeletal malformations and variations.

There were no mortalities and no treatment-related clinical signs or macroscopic findings. During the treatment interval (GD 6-18), decreased maternal body weight gains of 44% were observed at the HDT (300 mg/kg/day), as compared to controls. Further evaluation of this finding revealed that this percent reduction in body weight gain at the high dose level constitutes only a 95.8 gram difference in animals of greater than 4 kg mean body weight, is not of biological significance and no toxicity was observed associated with this finding. Also note that on gestation day 29, corrected body weights showed no effects at any dose level. No abortions were noted in this study at any dose level up to the HDT, 300 mg/kg/day.

In a range-finding developmental toxicity study, five females per dose level received dose levels of 100, 300, 750 and 1000 mg/kg/day (see Appendix to this DER) (MRID No. 00078797). In this study, abortion was observed in one doe at 100 mg/kg/day, 0 does at 300 mg/kg/day, 2 does at 750 mg/kg/day, and 2 does at 1000 mg/kg/day. During peer review of these data by RRB1, it was concluded that abortion was considered as maternal toxicity and a LOAEL was determined for this effect at 750 mg/kg/day. It is also noted that several other dams died at the 100 and 300 mg/kg/day dose level likely associated with dosing error. It is therefore unclear whether the abortions observed were also associated with dosing error or due to test material toxicity since no pathology data were available. Further, no abortions were observed at the 300 mg/kg/day dose level which is 3x the dose where abortion was first observed at the 100 mg/kg/day level, no abortion was observed in the definitive study at dose levels up to 300 mg/kg/day (HDT) and no dose response increase in the level of abortion was observed at the high dose level in this range-study.

Due to the increase in abortion observed in the range-finding study, the maternal LOAEL was established at 750 mg/kg/day. The maternal NOAEL is 300 mg/kg/day (HDT).

There were no complete litter resorptions at any dose level. Furthermore, there were no effects of treatment on numbers or percentages of resorptions, live fetuses, or dead fetuses, or on the number of litters, sex ratio, or post-implantation loss. Fetal body weights and length were unaffected by treatment. There were no treatment-related effects on skeletal ossification. There were no treatment-related external, visceral, or skeletal malformations or variations.

The developmental LOAEL was not observed. The developmental NOAEL is 300 mg/kg/day (HDT). Based on the results of the range-finding study, much higher dose levels should have been used in the definitive study (dose levels<750 mg/kg/day were supportable) and the fact that

no toxicity was observed in this study, this developmental toxicity study in the rabbit is considered inadequate to assess the potential developmental toxicity of sulfometuron methyl.

This study is classified **acceptable/non-guideline** and does not satisfy the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in rabbits. The study is considered non-guideline because dosing was considered inadequate, based on the lack of maternal toxicity observed at the highest dose level in the definitive study; the results of the range-finding study indicated that a dose less than 750 mg/kg/day would be appropriate for the definitive study.

A.3.3 Reproductive Toxicity

870.3800 Reproduction and Fertility Effects – Rat

No reproductive toxicity study is available in the data base and no study is required as this is not a food or feed use.

A.3.4 Chronic Toxicity

870.4100b Chronic Toxicity - Dog

In a chronic toxicity study in dogs (MRID No. 00129051), sulfometuron-methyl (98.8-100% a.i., Batch Nos. INT-5648-12 and INT-5648-13) was administered daily in the diet to 6 beagle dogs/sex/dose for 1 year at concentrations of 0, 200, 1000, or 5000 ppm (equivalent to 0/0, 5.2/5.3, 27.5/28.3, and 152.6/148.5 mg/kg/day in males/females). Additionally, a palatability study was completed where 1 dog/sex/dose was treated with the test compound in the diet at 5000 or 7500 ppm for 4 weeks.

No adverse, treatment-related effects were observed on mortality, clinical signs, food consumption, food efficiency, urinalysis or gross pathology. The 5000 ppm males lost weight during the first 4 weeks (-0.3 kg), when food consumption was similar to controls. In addition, overall body weight gain was also decreased in the 5000 ppm males (-1.3 kg treated vs 0.2 kg controls) at week 53. Due to the early reductions in body weight gain observed during weeks 0-2 and 0-4, it might be assumed that the reduction in gain could be associated with diet palatability but only a very slight and non-significant reduction in food consumption was apparent in males.

Sulfometuron methyl induces hemolytic anemia in male and female dogs. Statistically significant decreases ($p \leq 0.05$) in erythrocyte count, hemoglobin, and hematocrit were noted in the 5000 ppm males (↓13-17%) and in females at both the 1000 and 5000 ppm dose levels (↓8-10%) at 12 months. Decreases were apparent at other sampling intervals during the study, but no statistical assessment was performed at these other times. In addition, increases in platelet count were concurrently observed. Decreases in monocytes were observed in females at all dose levels at both the 6 month and 12 month assessment intervals, but not at the 9 month interval at any dose level. Therefore, it is unclear whether the observed effect on monocytes is a real manifestation of toxicity. Mildly increased hemosiderin was noted in the spleen of 3/6 females

at 5000 ppm vs 0/6 controls. These effects were considered indicative of hemolytic anemia and considered compound related.

Increased serum alkaline phosphatase levels were observed in the 5000 ppm males (↑11-113%) and females (↑26-181%). This increase grew in magnitude with the duration of treatment and was determined to be statistically different ($p \leq 0.05$) from the controls at 12 months in both males and females. Increased alkaline phosphatase was also apparent at the 1000 ppm level in females. However, statistical significance was only assessed at 12-months. Cholesterol was increased in the 1000 ppm females from 7-37% for months 1, 3, 6, 9 and 12 and in 5000 ppm females over the same sampling periods (↑14-33%) with statistical significance ($p \leq 0.05$) at the 12 month interval.

Statistically significantly increased ($p < 0.05$) absolute liver weights were noted in 5000 ppm females and increased relative liver weights were observed in male and female 5000 ppm groups. In the absence of associated histopathological changes in the liver, the increased liver weight might be considered compensatory and not adverse. In addition, increased absolute and relative thymus weights were noted in 5000 ppm females. Increased thymus weights were also observed in males at all dose levels but without an apparent dose response relationship.

At 5000 ppm, increased incidences of small prostate and mild atrophic acini in the prostate were noted (2/6 treated vs 0/6 controls). Testicular atrophy was noted in one control, one 1000 ppm male and two high dose males. Testicular degeneration was observed in one control, one 1000 ppm male and in three 5000 ppm males. The two animals with small prostate noted at necropsy, both had testes weights below the mean for the 5000 ppm group. The mean testes weight in the 5000 ppm group was 19.068 grams while the animals with the small prostate weights had testes weights of 18.22 and 17.28 grams. In addition, these same two animals were two of the three 5000 ppm males with testicular degeneration. Other organ weight changes were also observed but without clear dose-response relationships.

The NOAEL is 1000 ppm (equivalent to 27.5/28.3 mg/kg/day in males/females). The LOAEL was 5000 ppm (equivalent to 152.6/148.5 mg/kg/day in males/females, respectively) based on findings of hemolytic anemia, reduced body weight gain in males and increased serum alkaline phosphatase levels in both males and females.

This study is classified as **acceptable/guideline** and it satisfies the guideline requirement (OPPTS 870.4100b, OECD 452) for a chronic oral toxicity study in dogs. A number of deficiencies were apparent in the study but most are minor and do not impact upon acceptability of this study.

A.3.5 Carcinogenicity

870.4200a Carcinogenicity Study - rat

870.4200b or 83-2. Carcinogenicity (feeding) – Mouse

There are no carcinogenicity studies for sulfometuron methyl since sulfometuron methyl has no

food or feed tolerances and chronic exposure to this pesticide is unlikely, therefore, such studies are not required.

A.3.6 Mutagenicity

Gene Mutation

Gene Mutation	Salmonella/ Microsome assay	00078792 (1979) Acceptable/guideline in strains TA 1535, TA 1537, TA 98 and TA 100 in the presence or absence of activation.	No mutagenic activity for all strains of bacteria tested.
	Chinese Hamster Ovary	00078793 (1981) Acceptable/guideline CHO cell line was used to detect mutations for HGPRT	No mutagenic activity with or without activation.

Cytogenetics

Chromosome aberration	Chinese Hamster Ovary in vitro cytogenetic assay	00146846 (1981) Acceptable/guideline CHO in vitro assay with and without activation	No increase in chromosome damage and aberrations.

Other Genotoxicity

Un-scheduled DNA synthesis	Unscheduled DNA synthesis in rat hepatocytes *in vitro*	00146847 (1983) Acceptable/guideline	No induction of UDS was observed.

A.3.7 Neurotoxicity

870.6100 Delayed Neurotoxicity Study – Hen

870.6200 Acute Neurotoxicity Screening Battery

870.6200 Subchronic Neurotoxicity Screening Battery

870.6300 Developmental Neurotoxicity Study

Neurotoxicity testing is not required as there are no food or feed tolerances and no indications of neurotoxicity in any available studies.

A.3.8 Metabolism

870.7485 Metabolism - Rat

870.7600 Dermal Absorption – Rat

No dermal absorption data are available in the database.

A.3.9 Special/Other Studies.

Available data do not suggest the need for any special studies.

A.4 References (in MRID No. order)

00071412. Dashiell, O.L.; Henry, J.E. (1980) Eye Irritation in Rabbits, Haskell Laboratory Report No. 963-80. E.I du Pont de Nemours, Wilmington, Del.;CDL:244195-N. Unpublished.

00078792. Taylor, J.D. (1979) Mutagenic Activity in the Salmonella Microsome Assay: Haskell Laboratory Report No. 271-79. E.I. du Pont de Nemours & Co., Wilmington, Del.; CDL:245515-K. Unpublished.

00078793. Krahn, D.F.; Fitzpatrick, K. (1981) Chinese Hamster Ovary Cell Assay for Mutagenicity; Haskell Laboratory Report No. 1074-80. E. I. du Pont de Nemours & Co., Wilmington, Del.; CDL:245515-L. Unpublished.

00078796. Lu, M.H. (1981) Teratogenicity Study by Diet in the Rat with Benzoic acid, 2-(((((4,6-dimethyl-2-pyrimidinyl) amino) carbonyl)-amino)sulfonyl)-methyl ester: Haskell Laboratory Report No. 316-81. E.I. du Pont de Nemours & Co., Wilmington, Del.; CDL:245515-O. Unpublished.

00078798. Serota, D. G.; Fieser, S.; Durloo, R.S.; et al (1981) Teratology Study in Rabbits: H-13647-02: Benzoic Acid, 2-(((((4,6-dimethyl ester: Project No. 201-555; HLO-331-81. Hazleton Laboratories America, Inc., E.I. du Pont de Nemours & Co., Wilmington, Del.; CDL:245515-Q. Unpublished.

00126714. Dashiell, O.; Hinckle, L. (1983) Subacute Dermal Toxicity (21-days) in Rabbits: Haskell Laboratory Report No. 792-82. E.I du Pont de Nemours & Co., Wilmington, DE; CDL:249865-A. Unpublished.

00129051. Wood, C.; O'Neal, F. (1983) One-year Feeding Study in Dogs with Benzoic Acid, 2-(((((4,6-dimethyl-2-pyrimidinyl)-amin0)carbonyl) amino)sulfonyl)-Methyl Ester INT-

5648: Haskell Laboratory Report No. 482-82. E.I du Pont de Nemours & Co., Inc., Wilmington, DE; CDL:250590-A, Unpublished.

00146846. Galloway, S. (1981) Mutagenicity Evaluation of H#13,647-03 in an *in vitro* Cytogenetic Assay Measuring Chromosome Aberration Frequencies in Chinese Hamster Ovary (CHO) Cells: (Benzoic Acid, 2-((((4,6-dimethyl-2-pyrimidinyl) amino) carbonyl)amino)sulfonyl-methyl ester): Project No. 20990. Litton Bionetics, Inc. Unpublished.

00146847. Ford, L. (1982) Unscheduled DNA Synthesis/Rat Hepatocytes in vitro:(Benzoic Acid, 2-((((4,6-dimethyl-2-pyrimidinyl)amino)carbonyl)amino)-sulfonyl)-Methyl Ester): Haskell Laboratory Report No. 769-82. E.I du Pont de Nemours and Co., Unpublished.

41672808. Sarver, J. (1990) Primary Dermal Irritation Study with INT 5648-40 in Rabbits: Lab Project Number: 137-90: 4581-804. Haskell Laboratory. Unpublished.

43089201. Sarver, J. (1990) Oral LD50 Test with INT-5648-11 in Male and Female Rats: Lab Project Number: 0581-886: HLR 870-80. E.I. du Pont de Nemours and Co. Unpublished.

43089202. Sarver,J. (1990) Acute Skin Absorption LD50 with INT-5648-13 in Male and Female Rabbits: Lab Project Number 0581-907:HLR-1078-80. E.I du Pont de Nemours and Co. Unpublished.

43089203. O'Neill, A. (1990) Acute Inhalation Toxicity Study with INT-5648-18 in Rats: Lab Project Number: 0581-944: HLR-657-82. E.I. du Pont de Nemours and Co. Unpublished.

43089204. Sarver, J. (1990) Primary skin Irritation and Sensitization Test with INT-5548-03 on Guinea Pigs: Lab Project Number : 0581-790: HLR 232-79. E.I du Pont de Nemours and Co. Unpublished.

Appendix B: EPA Review of Human Research - Studies Reviewed for Ethical Conduct

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