MEMORANDUM


FROM: Judy Facey, Toxicologist 
       Reregistration Branch 2 
       Health Effects Division (7509C)

THROUGH: Jess Rowland, Co-Chair 
          and 
          Karen Whitby, Co-Chair 
          Hazard Identification Assessment Review Committee 
          Health Effects Division (7509C)

TO: Kelly O’Rourke, Risk Assessor 
    Registration Action Branch 3  
    Health Effects Division (7509C)

PC Code: 122009

On January 20, 2004, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for Mesosulfuron methyl with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to Mesosulfuron methyl was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996 in accordance with the 2002 OPP 10X Guidance Document. The conclusions drawn at this meeting are presented in this report.
Committee Members in Attendance

Members present were: William Burnam, Pamela Hurley, P. V. Shah, Karen Whitby (Co-Chair), William Dykstra, Jonathan Chen, Jessica Kidwell, John Liccione, Susan Makris, and Elizabeth Mendez

Member(s) in absentia: Brenda Tarplee (Executive Secretary), Ayaad Assaad, Jess Rowland (Co-Chair)

Data evaluation prepared by: Judy Facey, Ph.D. Reregistration Branch 2

Also in attendance were: Al Nielson, Pauline Wagner, Stephen Dapson, Paula Deschamp, Kelly O’Rouke, Nancy Dodd and Sarah Winfield

Data Evaluation / Report Presentation

Judy Facey, Ph.D.
Toxicologist

Secondary or Peer Review

Stephen Dapson, Ph.D.
Branch Senior Scientist/ Toxicologist
INTRODUCTION

On January 20, 2004, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for Mesosulfuron methyl with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational and/or residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to Mesosulfuron methyl was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996 in accordance with the 2002 OPP 10X Guidance Document.

I. FQPA HAZARD CONSIDERATIONS

1. Adequacy of the Toxicity Data Base
   The HIARC concluded that the toxicology database for mesosulfuron methyl is adequate for FQPA assessment. The database contains an acceptable/guideline two-generation reproductive toxicity study, one developmental toxicity study each in rats (oral) and rabbits (oral).

2. Evidence of Neurotoxicity
   The HIARC concluded that there is not a concern for neurotoxicity resulting from exposure to mesosulfuron methyl. Acute and subchronic neurotoxicity studies were not submitted. No signs of neurotoxicity were observed in the entire database for mesosulfuron methyl.

3. Developmental Toxicity Study Conclusions
   3.1 Prenatal Toxicity study in Rats (oral)

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 45430404), AE F 130060 (Mesosulfuron-methyl; 94.6-95.3% a.i.; Lot/Batch # 35316) in 1% (w/v) aqueous methyl cellulose was administered by oral gavage at a dose volume of 5 mL/kg bw/day to 23 female Hsd: Sprague Dawley SD rats/group at dose levels of 0, 100, 315, or 1,000 mg/kg on gestation days (GD) 7 through 16. All dams were sacrificed on GD 21 and their fetuses were removed by cesarean and examined.

There were no effects of treatment on maternal survival, clinical signs, body weight, body weight gain, food consumption, or gross pathology.

The maternal LOAEL was not observed. The maternal NOAEL is 1,000 mg/kg/day (limit dose).

There were no abortions, premature deliveries, fetal deaths, or complete litter resorptions. Similarly, there were no effects of treatment on the number of resorptions, number of fetuses (live or dead), post-implantation loss, fetal sex ratio, fetal body weights, placental weights, or crown-rump length. There were no external, visceral, or skeletal malformations or variations which could be unequivocally attributed to treatment. Bilateral non-ossification of metacarpal 5 of the forepaw was increased (p≤0.05) at 1,000 mg/kg (8% fetal incidence) over controls (3% fetal incidence); however, a greater incidence was noted in a historical control group (14% fetal
incidence), so this retardation was not considered treatment-related.

The developmental LOAEL was not observed. The developmental NOAEL is 1,000 mg/kg/day (limit dose).

This study is classified acceptable/guideline (OPPTS 870.3700a) and satisfies the requirements for a developmental study in the rat. The LOAEL was not observed; however, the compound was tested up to the limit dose.

3.2 Prenatal Toxicity study in Rabbits (Oral)

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 45386401) [AE F130060 (Mesosulfuron-methyl; 94.6% a.i., Batch/Lot # 35316) in 1% (w/v) aqueous methyl cellulose was administered by oral gavage at a dose volume of 5 mL/kg bw/day to 15 female Himalayan rabbits/dose at dose levels of 0, 100, 315 or 1000 mg/kg bw/day on gestation days (GD) 6 through 18. All dams were sacrificed on GD 29 and their fetuses were removed by cesarean and examined.

There were no effects of treatment on maternal survival, clinical signs, body weight, body weight gain, food consumption, or gross pathology.

The maternal LOAEL was not observed. The maternal NOAEL is 1000 mg/kg bw/day (limit dose).

There were no abortions, premature deliveries, or complete litter resorptions. Similarly, there were no effects of treatment on the number of resorptions, number of fetuses (live or dead), post-implantation loss, fetal sex ratio, fetal body weights, placental weights, or crown-rump length. There were no external, visceral, or skeletal malformations or variations which could be unequivocally attributed to treatment. Four dead fetuses (4/97) were observed in the high dose group, and two dead fetuses (2/90) occurred in the low dose group. These values are within historical range of the rabbit strain used.

The developmental LOAEL was not observed. The developmental NOAEL is 1000 mg/kg bw/day (limit dose).

This study is classified acceptable/ guideline and satisfies the requirements for a developmental toxicity study (OPPTS 870.3700; OECD 414) in rabbits. The LOAEL was not observed; however, the compound was tested up to the limit dose.

4. Reproductive Toxicity Study Conclusions

EXECUTIVE SUMMARY: In a two-generation reproduction study (MRID 45430405) 25 Sprague Dawley: SD/sex/dose were exposed to AE F130060 (Mesosulfuron-methyl; 94.6% a.i.; Lot/Batch #: 35316) in the diet at concentrations of 0, 160, 1,600, or 16,000 ppm (equivalent to 0, 11.7, 115.3, and 1175.2 mg/kg/day in males and 0, 13.5, 132.6 and 1387.6 mg/kg/day in females, respectively). Two litters were produced by each generation. All P, and F1 generation
parental rats received the test compound mixed in diet or the diet without test substance (control),
during a 10 week premating period and during the mating period. The parental animals was then
paired for mating to produce the A litters. In the P and F1 generation females, treatment was
continued throughout gestation and three week lactation period for the F1a and F2a litters. Since
the number of F1a litters in the P generation of the low dose group and the F1 parents of the
intermediate and highest dose groups did not yield 20 litters, a second mating was initiated. The
same P generation rats were allowed a 2-3 week rest period prior to cohabitation to produce the
F1b litter. Similarly all the F1 generation rats were allowed a 2-3 week rest period prior to
cohabitation to produce the F2b litter. All parental males and females received the test substance
until schedule sacrifice.

There were no treatment related deaths or clinical findings in any of the parental males and
females. The observed deaths were single incidents, occurred during various phases of the study
without dose relationships, and were considered to be of spontaneous origin and not treatment
related.

Small subcutaneous abscesses forming scabby wounds after bursting were noted in males and
females, in all groups, including the control. These lesions were primarily located in the ventral
abdominal, genital or inguinal regions or on the ventral part of the neck and head or on the mouth.
The subcutaneous abscesses were considered to be probably due to an endemic bacterial infection,
which in general did not markedly affect the health status of the animals or compromise the study.

There were no dose - or treatment related effects on body weights, body weight gains, food
consumption, organ weight or food efficiency.

The parental systemic NOAEL is 16,000 ppm (HDT) (1175.2 mg/kg bw/day in males,
1387.6 mg/kg bw/day in females, respectively). The parental systemic LOAEL was not
determined.

Mortality in pups was generally preceded or accompanied by poor suckling pups, but not by ill
health. There were only single cases of clinical findings (hypoactivity, paleness, swelling of a
pup's whole body or abdomen) which could be related to individual cases of mortality. Mortality
and the related findings were observed with similar frequency and with a similar pattern in all
experimental groups, including the control group. Mortality in the F2a pups was also comparable
with that in the F1a and F1b pups.

Evaluation of organ weights showed a statistically significant higher relative thymus weight
(112%) in high dose F1b female pups and relative spleen (19%) and ovary weights (114%) of the
high dose F2b pups were also slightly higher as compared to the corresponding control values.
However, the deviations from the control were small and similar organ weight changes were not
observed in the F1a and F2a pups. Histological examination did not reveal any test substance
related tissue change on the spleen and ovaries.

The offspring NOAEL is >16000 ppm (1175.2 mg/kg bw/day in males, 1387.6 mg/kg bw/day
in females, respectively). The offspring LOAEL was not determined.

Mating performance, fertility, and pup growth and survival were not affected by AE F130060
treatment in the F1 and F2 generations. All males inseminated their allocated female during the first to 4th estrus during the first cohabitation and during the 1st and 5th estrus during the second period. The pregnancy indices for the F generation were 88, 72, 84 and 88% for the first cohabitation period and 87, 83, 80, and 92% for the second cohabitation period in the control group, and the 160, 1600, and 16,000 ppm groups, respectively. The pregnancy indices were similar for the F1 generation rats.

Therefore, the reproductive NOAEL is \( \geq 16000 \) ppm (1175.2 mg/kg bw/day in males, 1387.6 mg/kg bw/day in females, respectively). The reproductive LOAEL was not determined.

This study is classified acceptable/ guideline and satisfies the guideline requirement for a two-generation reproductive study (OPPTS 870.3800; OECD 416 in [rats]).

5. **Additional Information from Literature Sources**: None

6. **Pre-and/or Postnatal Toxicity**

   **A. Determination of Susceptibility**

   The data available for evaluation suggest that there is no evidence of increased quantitative or qualitative susceptibility of the offspring after in utero or post-natal exposure to mesosulfuron methyl. Neither acceptable Developmental Toxicity Studies in rats or rabbits revealed increased susceptibility of the fetus after in utero exposure. Similarly, the results of the Two Generation Reproduction Toxicity Study did not indicate an increased susceptibility to the test article in utero or during post-natal exposure.

   **B. Degree of Concern Analysis and Residual Uncertainties**

   There are no concerns or residual uncertainties for pre and/ or post natal toxicity.

   **C. Proposed Hazard-based Special FQPA Safety Factor(s):**

   Based on the above-described data, no special FQPA safety factor (i.e. 1X) is required since there are no residual uncertainties for pre and/ post natal toxicity.

*NOTE:* The Special FQPA Safety Factor recommended by the HIARC assumes that the exposure databases (dietary food, drinking water, and residential) are complete and that the risk assessment of each potential exposure scenario includes all metabolites and/ or degradates of concern and does not underestimate the potential risk for infants and children.

7. **Recommendation for a Developmental Neurotoxicity Study**

   The HIARC concluded that there is not a concern for developmental neurotoxicity resulting from exposure to mesosulfuron methyl.
A. Evidence that suggest requiring a Developmental Neurotoxicity study:

- None.

B. Evidence that do not support a need for a Developmental Neurotoxicity Study:

- There is no evidence of neurotoxicity or neuropathology in the available toxicity studies.

II. HAZARD IDENTIFICATION

1. Acute Reference Dose (RfD)

An effect of concern attributable to a single exposure (dose) was not identified from the oral toxicity studies including developmental toxicity studies in rats and rabbits.

2. Chronic Reference Dose (cRfD)

**Study Selected**: Chronic Oral Toxicity Study in Dogs

**MRID No.**: 45386330

**Executive Summary**: In a chronic toxicity study (MRID 45386330) 6 Beagle dogs/sex/dose were exposed to AE F130060 (Mesosulfuron-methyl; 95.3 -95.7 % a.i.; Lot/Batch #: not reported) in the diet at concentrations of 0, 400, 4000, or 16,000 ppm (equivalent to 0, 14.7, 155, and 574 mg/kg/day in males and 0, 15.3, 169, and 646 mg/kg/day in females, respectively) for up to 12 months.

Mortality, clinical signs, body weight, body weight gain, food consumption, ophthalmoscopic findings, hematology, clinical chemistry, urinalysis, and organ weights for both sexes at all doses were unaffected by treatment.

At the high dose level (16,000 ppm) 3/6 males had minimal to slight, and minimal, increased mucus secretion in the cardiac and fundic sections of the stomach. In one of these animals the increased secretion was accompanied by chronic superficial gastritis. There were no treatment-related histopathological changes in females at 16,000 ppm, or in males and females dogs at the lower dose levels.

Therefore, the LOAEL is 16,000 ppm (equivalent to 574 mg/kg/day in males), based on the increased mucus secretion in the cardiac and fundic sections of the stomach of the males dogs (HDT) and chronic superficial gastritis (1/6). The NOAEL is 4000 ppm (equivalent to 155 mg/kg/day in males).

This study is classified acceptable/guideline and satisfies the guideline requirements [OPPTS 870.4100, OECD 452] for a chronic study in dogs.
Dose and Endpoint for Establishing cRfD: A NOAEL of 155 mg/kg/day based on increased mucus secretion in the cardiac and fundic sections of the stomach and chronic superficial gastritis in males at 574 mg/kg/day (LOAEL).

Uncertainty Factor(s): 100 (10x for interspecies extrapolation and 10x for intraspecies variations).

Comments about Study/Endpoint/Uncertainty Factor: The study duration and route of exposure are appropriate for this risk assessment.

\[
\text{Chronic RfD} = \frac{155 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}} = 1.55 \text{ mg/kg/day}
\]

3. Incidental Oral Exposure: Short-Term (1-30 days) and Intermediate-Term (1 - 6 Months)

A dose/endpoint was not selected since there are no residential uses were proposed at this time. In addition, no oral toxicity of concern was seen in any of the available studies for these scenarios. The oral LD₅₀ is ≥ 5000 mg/kg/day.

4. Dermal Absorption

Dermal Absorption Factor:

A dermal absorption factor is not needed since quantification is not required either for the non-cancer or cancer dermal risk.

NOTE: An unacceptable/nonguideline dermal penetration study in rats (MRID 45386416) was conducted with the test article. The study was classified unacceptable due to the excessive amount of test material remaining on the application site dressings at six hours which material is unavailable for absorption. However, because the test material used is similar to the mixed formulation (i.e., methylated oil) that will be used in the field, this study could be used to establish a dermal absorption factor if needed.

5. Dermal Exposure

Comments about Study/Endpoint: No hazard identified. Quantification of dermal risk assessment is not required for this exposure due to the lack of dermal, systemic, neuro or developmental toxicity concerns.

6. Inhalation Exposure (All Durations)
Study Selected: Chronic Oral Toxicity Study in Dogs §870.4100b

MRID No.: 45386330

Executive Summary: See Section II.2 (cRfD)

Dose and Endpoint for Risk Assessment: A NOAEL of 155 mg/kg/day based on increased mucus secretion in the cardiac and fundic sections of the stomach, and chronic superficial gastritis (1/6) in males at 574 mg/kg/day (LOAEL).

Comments about Study/Endpoint/Uncertainty Factor: Due to the lack of a repeated dose inhalation toxicity study, an oral study was selected. Absorption via inhalation is assumed to be equivalent to oral absorption.

7. Margins of Exposure
Summary of target Margins of Exposure (MOEs) for risk assessment.

<table>
<thead>
<tr>
<th>Route</th>
<th>Short-Term (1-30 Days)</th>
<th>Intermediate-Term (1 - 6 Months)</th>
<th>Long-Term (&gt; 6 Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Occupational (Worker) Exposure</td>
<td></td>
</tr>
<tr>
<td>Inhalation</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

For occupational exposure short-, intermediate-, and long-term inhalation exposure risk assessment, a MOE of 100 is adequate. This is based on the conventional uncertainty factor of 100X, which includes the 10X for intraspecies extrapolation and 10X for interspecies variation.

No residential uses are proposed for mesosulfuron methyl at the present time.

8. Recommendation for Aggregate Exposure Risk Assessments

As per FQPA, 1996, when there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. An aggregated exposure risk assessment is not required since there are no residential uses for mesosulfuron methyl at this time.
III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

1. Combined Chronic Toxicity/Carcinogenicity Study in Rats

MRID No. 45430402

Executive Summary
In a combined chronic toxicity/carcinogenicity study (MRID 45430402), 70 Wistar rats/sex/dose were exposed to AE F130060 (Mesosulfuron-methyl; 94.6-95.7 % a.i.; Lot/Batch #: 35316) in the diet at concentrations of 0, 160, 1,600, or 16,000 ppm (equivalent to 0, 7.46, 73.8, and 764 mg/kg/day in males and 0, 9.39, 94.7 and 952 mg/kg/day in females, respectively) for up to 24 months. An additional group of 10 rats/sex/dose were similarly treated and sacrificed at 12 months.

Mortality, clinical signs, body weight, body weight gain, food consumption, ophthalmoscopic findings, hematology, clinical chemistry, urinalysis, organ weights, gross pathology, and histopathology for both sexes at all doses were unaffected by treatment.

The LOAEL was not observed. The NOAEL is 16,000 ppm (equivalent to 764/952 mg/kg/day in males/females).

At the doses tested, there was not a treatment related increase in tumor incidence when compared to controls. Dosing was considered adequate, as the high dose approximated the limit dose.

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

Discussion of Tumor Data
There were no treatment-related increases in any tumor type in either sex of rats.

Adequacy of the Dose Levels Tested
Although no systemic toxicity was observed, dosing was considered adequate in both sexes since the high dose approached the limit dose.
2. Carcinogenicity Study in Mice

MRID No. 45430403

Executive Summary: In a carcinogenicity study (MRID 45430403), 50 Crl:CD-1® (ICR)BR mice/sex/dose were exposed to AE F130060 (mesosulfuron-methyl; 94.6-95.3% a.i.; Lot/Batch #: Pfl; 35316) in the diet at concentrations of 0, 80, 800, or 8000 ppm (equivalent to 0/0, 10.6/13.9, 102.8/129.8, and 1069.4/1355.6 mg/kg/day in males/females) for up to 18 months. An additional group of 10 mice/sex/dose were similarly treated and sacrificed at 12 months.

No treatment-related effect was observed on mortality, clinical signs, body weight, body weight gain, food consumption, hematology, clinical chemistry, organ weights, or gross and histologic (including tumors) pathology. An adverse effect was not observed at any dose in either sex.

The LOAEL was not observed. The NOAEL is 8000 ppm (equivalent to 1069.4/1355.6 mg/kg/day in males/females).

At the doses tested, there was not a treatment-related increase in tumor incidence when compared to controls. Dosing exceeded the limit dose.

This study is classified as acceptable/guideline and satisfies the guideline requirements (OPPTS 870.4200b; OECD 451) for a carcinogenicity study in mice.

Discussion of Tumor Data
There were no treatment-related increases in any tumor type in either sex of rats.

Adequacy of the Dose Levels Tested
Although no systemic toxicity was observed, dosing was considered adequate in both sexes since the highest dose tested exceeded the limit dose.

3. Classification of Carcinogenic Potential
In accordance with 1999 Draft Carcinogen Risk Assessment Guidelines (July 1999), the HIARC classified Mesosulfuron methyl as “not likely to be carcinogenic to humans” based on the lack of evidence of carcinogenicity in the rat and the mouse.
IV. MUTAGENICITY
The HIARC concluded that there is not a concern for mutagenicity resulting from exposure to Mesosulfuron methyl.

The following table illustrates the mutagenicity/genetic toxicity data base for Mesosulfuron methyl that has been classified as acceptable and selected to be representative.

<table>
<thead>
<tr>
<th>MRID/Date</th>
<th>STUDY</th>
<th>STUDY REPORT NO.</th>
<th>REPORTED RESULT</th>
</tr>
</thead>
<tbody>
<tr>
<td>45386402 (11/20/03)</td>
<td>Bacterial reverse mutation assay</td>
<td>A56743: 96.0122</td>
<td>Negative ± S9 up to cytotoxic 5000 µg/plate</td>
</tr>
<tr>
<td>45386404 (11/20/03)</td>
<td>CHO/HGPRT Parent compound</td>
<td>A67081: 97.0820</td>
<td>Negative ± S9 up to cytotoxic 2500 µg/mL and precipitation 250 µg/mL</td>
</tr>
<tr>
<td>45386406 (11/20/03)</td>
<td>In Vivo MT Parent compound</td>
<td>A67143: 97.0763</td>
<td>Negative at highest dose test (limit dose) 2000 mg/kg.</td>
</tr>
<tr>
<td>45386403 (11/20/03)</td>
<td>In Vitro CA Parent compound</td>
<td>A67555: 98.0128</td>
<td>Negative ± S9 precipitation ≥ 100 µg/mL.</td>
</tr>
<tr>
<td>45386405 (11/20/03)</td>
<td>In Vitro UDS Parent compound</td>
<td>A67689: 98.0168</td>
<td>Negative ± S9 up to ≥ 100 µg/mL.</td>
</tr>
</tbody>
</table>

CHO/HGPRT = Mammalian cell forward mutation at the hypoxanthine-guanine phosphoribosyl transferase locus in Chinese hamster ovary cells.

In Vivo MT = Micronucleus test in rodents.

In Vitro CA = Chromosome aberrations in mammalian cells.

In Vitro UDS = Unscheduled DNA synthesis in mammalian cells.
IV. HAZARD CHARACTERIZATION

Acute toxicity
Mesosulfuron methyl is a non-irritant chemical, with a low acute toxicity (toxicity category III or IV) via the oral (IV), dermal (IV), or inhalation (III) routes of exposure. Mesosulfuron methyl is not a skin irritant (IV) and irritation that occurred in the eye (III) cleared up 48 hours after exposure.

Subchronic toxicity
There are no primary target organs identified from exposure to mesosulfuron methyl in the subchronic mice, rat or dog studies.

Chronic toxicity
There are no primary target organs from exposure to mesosulfuron methyl in the chronic dog or combined chronic/carcinogenicity rat studies. Increase mucus secretion in the cardiac and fundic sections of the stomach, and chronic superficial gastritis (1/6) was noted in the chronic toxicity study in dogs.

FQPA
There was no evidence of increased susceptibility of the young animals following exposure to mesosulfuron methyl in any of the developmental toxicity studies or the 2-generation reproduction study in the database.

Neurotoxicity
There was no evidence of mesosulfuron methyl-induced neurotoxicity in any study submitted.

Carcinogenicity
Mesosulfuron methyl has no carcinogenic potential, as indicated in both the rat and the mouse carcinogenicity studies. It is “not likely to be a human carcinogen” based on the lack of evidence of carcinogenicity in both the rat and the mouse.

Mutagenicity
Mesosulfuron methyl has no mutagenicity potential, based on several in vivo and in vitro studies.

Metabolism
Metabolism studies in rats indicated that mesosulfuron methyl onset of absorption was quick, but the quantity absorbed was low. The feces was the major route of excretion on both sexes (parent and metabolite AE F140584). The highest tissue residue levels were found in the plasma, blood, and liver. Metabolism of mesosulfuron methyl involved amidases (breakdown of the sulfonyleurea-bridge), hydroxylation, demethylation and hydrolysis.
V. DATA GAPS / REQUIREMENTS
A 28-Day Inhalation Toxicity (870.3465) study with the active ingredient.
VI. **ACUTE TOXICITY**

<table>
<thead>
<tr>
<th>Guideline No.</th>
<th>Study Type</th>
<th>MRID #(#(S))</th>
<th>Results</th>
<th>Toxicity Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>81-1</td>
<td>Acute Oral in Rats</td>
<td>45386321</td>
<td>(LD_{50} &gt; 5000 \text{ mg/kg} ) [M/F]</td>
<td>IV</td>
</tr>
<tr>
<td>81-2</td>
<td>Acute Dermal in Rats</td>
<td>45386322</td>
<td>(LD_{50} &gt; 5000 \text{ mg/kg} ) [M/F]</td>
<td>IV</td>
</tr>
<tr>
<td>81-3</td>
<td>Acute Inhalation in Rats</td>
<td>45386323</td>
<td>(LC_{50} &gt; 1.33 \text{ mg/kg} ) [M/F]</td>
<td>III</td>
</tr>
<tr>
<td>81-4</td>
<td>Primary Eye Irritation in Rabbits</td>
<td>45386324</td>
<td>Conjunctival irritation at 24 hrs in 1/3 which cleared by 48 hrs.</td>
<td>III</td>
</tr>
<tr>
<td>81-5</td>
<td>Primary Skin Irritation in Rabbits</td>
<td>45386325</td>
<td>Non Irritant</td>
<td>IV</td>
</tr>
<tr>
<td>81-6</td>
<td>Dermal Sensitization in Guinea Pigs</td>
<td>45386326</td>
<td>Unacceptable</td>
<td>Negative *</td>
</tr>
</tbody>
</table>

* There was no indication that the material is a dermal sensitizer; however, the study is unacceptable because the submitted positive control study was not conducted within 6 months of the sensitization study (i.e., they were approximately 9 months apart).
<table>
<thead>
<tr>
<th>Exposure Scenario</th>
<th>Dose Used in Risk Assessment, UF</th>
<th>Special FQPA SF* and Level of Concern for Risk Assessment</th>
<th>Study and Toxicological Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Dietary: All Population</td>
<td>An endpoint attributable to a single dose was not identified in the database.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic Dietary: All populations</td>
<td>NOAEL = 155 mg/kg/day, UF = 100 Chronic RfD = 1.55 mg/kg/day</td>
<td>FQPA SF = 1X cPAD = chronic RfD FQPA SF = 1.55 mg/kg/day</td>
<td>Chronic oral toxicity study in dogs. LOAEL = 574 mg/kg/day [M] based on increase mucus secretion in the cardiac and fundic sections of the stomach, and chronic superficial gastritis (1/6) of males dogs.</td>
</tr>
<tr>
<td>Incidental Oral: Short and Intermediate-Term)</td>
<td>No Residential Uses are Proposed for Mesosulfuron methyl.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermal Exposure: Short, Intermediate and Long Term</td>
<td>No hazard identified. Quantification of dermal risk is not required since there was no dermal, systemic, neuro or developmental toxicity.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhalation Exposure: Short, Intermediate and Long-Term</td>
<td>Oral NOAEL = 155 mg/kg/day (100% Oral Absorption Factor) Residential LOC for MOE = NA Occupational LOC for MOE = 100</td>
<td></td>
<td>Chronic oral toxicity study in dogs. LOAEL = 574 mg/kg/day [M] based on increase mucus secretion in the cardiac and fundic sections of the stomach, and chronic superficial gastritis (1/6) of males dogs.</td>
</tr>
<tr>
<td>Cancer (oral, dermal, inhalation)</td>
<td>“Not likely a human carcinogen” based on the lack of evidence of carcinogenicity in the rats and mice.</td>
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</tr>
</tbody>
</table>

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

**NOTE:** The Special FQPA Safety Factor recommended by the HIARC assumes that the exposure databases (dietary food, drinking water, and residential) are complete and that the risk assessment for each potential exposure scenario includes all metabolites and/or degradates of concern and does not underestimate the potential risk for infants and children.