HED DOC NO. 012517

**DATE:** **February 26, 1998**

**MEMORANDUM**

**SUBJECT:** ***HALOSULFURON-METHYL*** - Report of the Hazard Identification Assessment Review Committee.

**FROM:** Jess Rowland
Executive Secretary,
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

**THROUGH:** K. Clark Swentzel, Chairman,
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)
and
Mike Metzger, Co-Chairman
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

**TO:** Rick Loranger, Branch Senior Scientist
Registration Action Branch 2
Health Effects Division (7509C)

**PC Code: 128721**

On February 10, 1998, the Health Effects Division's Hazard Identification Assessment Review Committee evaluated the toxicology data base of halosulfuron-methyl and re-assessed the existing Reference Dose (RfD) and the toxicological endpoints selected for acute dietary as well as occupational and residential exposure risk assessments. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to halosulfuron as required by the Food Quality Protection Act (FQPA) of 1996. The Committee's conclusions are presented in this report.

Committee Members in Attendance

Members present were Karl Baetcke, William Burnam, Robert Fricke, Karen Hamernik, Susan Makris, Mike Metzger, John Redden, Jess Rowland (Executive Secretary) and Clark Swentzel (Chairman). Member in absentia was Melba Morrow. Data was presented by John Whalan of Registration Action Branch 2.

Data Presentation: _____
John Whalan
Toxicologist

Report Preparation: _____
Jess Rowland.
Executive Secretary

## I. INTRODUCTION

On September 23, 1993 the Health Effects Division's RfD/Peer Review Committee established a Reference Dose (RfD) of 0.1 mg/kg/day based on a NOEL of 10 mg/kg/day established in a chronic feeding study and an Uncertainty Factor of 100 for inter-species exptrapolation and intra-species variability (*Memorandum*: G. Ghali, HED to Joanne Miller, RD, dated January 31, 1994).

On February 20, 1994, the Health Effects Division's Toxicology Endpoint Selection (TES) Committee selected the doses and endpoints for acute dietary as well as occupational and residential exposure risk assessments (TES Document dated 5/14/96).

On February 10, 1998, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) re-assessed the existing RfD and the toxicology endpoints selected for acute dietary as well as occupational and residential exposure risk assessments pursuant to the Food Quality Protection Act (FQPA) of 1996. The application of the FQPA safety factor for the protection of infants and children from exposure to hallosulfuron, as required by FQPA, will be determined during risk characterization.

**This report supersede the previous RfD and TES Committee reports.**

## II. HAZARD IDENTIFICATION

### A. Acute Dietary

Study Selected: Developmental Toxicity - Rabbit §83-3b

MRID. Nos. 42139426

Executive Summary: In a prenatal developmental toxicity study, pregnant New Zealand white rabbits received oral (gavage) administrations of halosulfuron-methyl (98.5%) in aqueous carboxymethylcellulose and Tween 80 at doses of 0, 15, 50, or 150 mg/kg/day on gestation days 6-19. For maternal toxicity, the NOEL was 50 mg/kg/day and the LOEL was 150 mg/kg/day based on decreased body weight gain, food consumption, and food efficiency. For developmental toxicity, the NOEL was 50 mg/kg/day and the LOEL was 150 mg/kg/day based on decreased mean litter size, increased number of resorptions (total and per dam) and increased postimplantation loss. The Committee noted that these developmental findings, while not statistically significant, defined a consistent pattern of effect.

Dose and Endpoint for Risk Assessment: Developmental NOEL = 50 mg/kg/day based on decreased mean litter size, increased number of resorptions (total and per dam) and increased postimplantation loss at 150 mg/kg/day (LOEL).

Comments about Study and Endpoint: The Committee recommended that this dose and effect should be used for assessing acute dietary risks for the sub-populations, Females 13+ as well as Infants and Children. Although, the endpoint is developmental toxicity occurring *in utero*, and thus may not be suitable for use in risk assessment for Infants and Children, the Committee determined that it is appropriate to use for this subpopulation (Infants and Children) because there is evidence of alteration to the development of the fetal nervous system in the developmental toxicity study in rats. In that study, oral administration resulted in the occurrence of dilation of the lateral ventricles, dilation of the third ventricle, spinal cord agenesis, and adrenal agenesis at 750 mg/kg/day and malformed brain cortex at 250 mg/kg/day. Thus, the Committee determined that potential effects on functional development mandate the use of this endpoint for females of child bearing age (Females 13+) as well as for infants and children.

This endpoint is not applicable for Adult Males. A dose and endpoint was not identified for this subpopulation since there were no toxicological effects applicable to adult males and attributable to a single exposure (dose) were observed in oral toxicity studies including the developmental toxicity studies in rats and rabbits.

Uncertainty Factor (UF): 100 (10x for inter-species extrapolation and 10 x for intra-species variability).

$$\textbf{Acute RfD} = \frac{\text{50 mg/kg/day (NOEL)}}{\text{100 (UF)}} = \textbf{0.5 mg/kg/day}$$

**This risk assessment is required.**

**B. Chronic Dietary [Reference Dose (RfD)]**

The RfD established in 1993 was re-assessed by this Committee pursuant to the FQPA and is discussed below:

Study Selected: Chronic Toxicity - Dog §83-1b

MRID No. 42396211

Executive Summary: In a chronic toxicity study, groups of Beagle dogs (6/sex/dose) received gelatin capsules containing halosulfuron-methyl (98.7%) at 0, 0.25, 1.0, or 40 mg/kg/day for 52 weeks. Evaluations included observations for mortality, clinical toxicity, body weight and body weight gain, food consumption and efficiency, hematology and serum chemistry, organ weights, and macroscopic and microscopic pathology.

In large part, there were no apparent signs of clinical toxicity from administration of test article in male or female dogs. The incidence and frequency of soft feces and emesis appeared to increase in male dogs with increasing dose, but these would not be considered serious clinical manifestations of test article toxicity. One male dog at 40 mg/kg/day displayed signs of ataxia during week 18 of the study, and was later observed to display prostration and languid behavior. It is not readily apparent if the signs observed in this one dog were related to halosulfuron, as there were no other dogs manifesting these symptoms. Female dogs did not display significant clinical toxicity at any dose tested.

Body weight changes were limited to a decrease in body weight gain of approximately 19% in male dogs at the 10 mg/kg/day level during the weeks 0-13 of the study, and a decrease of approximately 21% in body weight gain in male dogs at the 40 mg/kg/day dose level for weeks 0-13 of the study. In female dogs, a 16% decrease in overall body weight gain was observed for weeks 0-51 of the study at the 40 mg/kg/day dose level.

Decreased red cell count, hemoglobin, and hematocrit were reported in female dogs at 40 mg/kg/day. Decreases of between 8-13% were observed for these parameters at 40 mg/kg/day. These changes are considered related to treatment in that the results from this dose group are substantially different than those observed in control female dogs. In male dogs during weeks 26 and 52 of the study, lymphocyte counts were decreased between 21-30% at 10 mg/kg/day and were decreased up to 56% at 40 mg/kg/day as compared to controls. Serum chemistry was minimally affected in male and female dogs, but significant decreases in serum cholesterol were observed in male dogs at 10 and 40 mg/kg/day.

No significant changes were observed in absolute or relative organ weights or in the results of urinalysis. Macroscopic and microscopic examination of tissues and organs showed no definitive effect of treatment. The presence of pituitary cysts in female dogs treated with 40 mg/kg/day was increased from control (2/6 vs 0/6). This was discussed by the registrant as being very close to historical control range (33.3% in the present study vs 28.9%). It is not possible to reach a definitive conclusion from these data, although it is noted that in the subchronic study (Nissan Chemical Industries, Ltd., 1991) an increased incidence of this lesion was not found.

At the September 23, 1993 meeting the RfD/Peer Review Committee determined that the NOEL and LOEL for this study should be 10 and 40 mg/kg/day, respectively, rather than the NOEL/LOEL of 1.0/10 mg/kg/day established in the Data Evaluation Record. This conclusion was based on the fact that the decrease in body weight gain in males was only observed during weeks 0-13 and that the overall weight gain for the 0-52 week treatment period was not significantly affected. It was also concluded that the decrease in cholesterol level without changes in other clinical parameters is of no toxicological significance. Therefore, for chronic toxicity, the NOEL was 10 mg/kg/day and the LOEL was 40 mg/kg/day based on decreased body weight gains and changes in hematological and blood chemistry parameters in female dogs.

Dose/Endpoint for establishing the RfD: NOEL=10 mg/kg/day based decreased body weight gains and changes in hematological and blood chemistry parameters in females at 40 mg/kg/day (LOEL).

Comments about Study and Endpoint: The RfD was confirmed by the Agency RfD Workgroup on February 17, 1994. The HIARC re-affirmed the dose and endpoints selected for establishing the RfD.

Uncertainty Factor (UF): 100 (10 x for inter-species extrapolation and 10 x for intra-species variability).

$$\textbf{Chronic RfD} = \frac{\text{10 mg/kg/day (NOEL)}}{\text{100 (UF)}} = \textbf{0.1 mg/kg/day}$$

## C. Occupational/Residential Exposure

### 1. Dermal Absorption

No dermal absorption studies are available. The Committee estimated a dermal absorption rate of 75% based on the results of an oral developmental toxicity and a 21-day dermal toxicity studies in the same species (rats).

In the oral developmental toxicity study in rats, the maternal NOEL was 250 mg/kg/day and the LOEL was 750 mg/kg/day based on decreases in body weight gains and food consumption (MRID No. 42139425).

In the 21-day dermal toxicity study in rats, the systemic toxicity NOEL was 100 mg/kg/day and the LOEL was 1000 mg/kg/day based on decreased body weight gain in males (42661417).

A ratio of the LOELs from the oral and dermal studies, indicated an approximate dermal absorption rate of 75% (oral LOEL 750 mg/kg/day ÷ dermal LOEL of 1000 x 100 = 75%)

Dermal Absorption Factor: 75% (estimated)

### 2. Short-Term Dermal - (1-7 days)

Study Selected: Developmental Toxicity-Rabbit §83-3b

MRID No. 42139426
Executive Summary: See Acute Dietary

Dose and Endpoint for Risk Assessment: Developmental NOEL=50 mg/kg/day based on decreased mean litter size, increased number of resorptions (total and per dam) and increased postimplantation loss at 150 mg/kg/day (LOEL).

Comments about Study and Endpoint: A 21-day dermal toxicity study in rats is available. The Committee, however, selected a developmental NOEL because: 1) of the consistent pattern in the fetal effects (decreased mean litter size, increased number of resorptions and increased postimplantation loss) observed in two species (rats and rabbits) via the oral route; 2) the developmental effects are considered acute effects and thus were appropriate for this exposure period (i.e., 1-7 days) of concern; 3) the reproductive/fetal parameters are not evaluated in the dermal toxicity study and thus the consequences of these effects cannot be ascertained for the dermal route of exposure; and 4) this endpoint will provide adequate protection for the subpopulation Female 13 + (i.e., pregnant workers)..

Since an oral NOEL was selected a dermal absorption factor of 75% should be used for this dermal risk assessment.

**This risk assessment is required.**

**3. Intermediate-Term Dermal (7 Days to Several Months)**

Study Selected: Chronic Toxicity-Dog §83-1b

MRID No. 42396211

Executive Summary: See Chronic Dietary

Dose and Endpoint for Risk Assessment: NOEL=10 mg/kg/day based on a decrease of approximately 21% in body weight gain in males at 40 mg/kg/day.

Comments about Study and Endpoint: At 40 mg/kg/day, decreases in body weight gain were seen during Study Weeks 0-13 in both sexes with the decrease being more pronounced in males (21%) than females (7%). However, overall weight gain for the entire study (0-52 Week) was not significantly affected in male dogs, but was decreased by 16% in female dogs at this dose. The Committee selected this dose and endpoint for this risk assessment due to the alterations observed in body weights parameters in both sexes during various phases of the study and thus meet the exposure period of concern (i.e., One-Week to Several Months).
Since an oral NOEL was selected, a dermal absorption factor of 75% should be used for this dermal risk assessment.

**This risk assessment is required.**

**4. Long-Term Dermal (Several Months to Life-Time)**

Study Selected: Chronic Toxicity-Dog §83-1b
MRID No. 42396211

Executive Summary: See Chronic Dietary

Dose and Endpoint for Risk Assessment: NOEL=10 mg/kg/day based decreased body weight gains and changes in hematological and blood chemistry parameters in females at 40 mg/kg/day (LOEL).

Comments about Study and Endpoint: This dose and endpoint was used for deriving the RfD. Since an oral NOEL was selected a dermal absorption factor of 75% should be used for this dermal risk assessment.

**This risk assessment is required.**

**5. Inhalation Exposure (Any-Time period)**

Based on the low acute toxicity ($LC_{50}$->6 mg/L, Tox. Cat. IV) and the use pattern (1 oz a.i/acre) there is minimal concern for potential inhalation exposure or risk.

This risk assessment is **NOT** required.

**D. Recommendation for Aggregate Exposure Risk Assessments**

An oral NOEL was selected for calculating the MOE's from oral and dermal exposures. The dermal exposure, using a dermal absorption factor of 75% should be converted to oral equivalent doses. Therefore,

For **acute** aggregate exposure risk assessment, combine the high end exposure values from food + water and compare it to the oral NOEL to calculate the MOE.

For **short, intermediate and chronic** aggregate exposure risk assessment, combine the average exposure values from food + water together with the aggregate exposures from dermal and compare it to the oral NOEL to calculate the MOE.

## III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

1. Combined Chronic Toxicity/Carcinogenicity Study-Rats §83-5

MRID No. 42661418

Executive Summary: Groups of male and female Crl:CD BR rats were fed diets containing halosulfuron-methyl (98.5%) at 0, 10, 100, 1000 or 2,500 ppm for 104 weeks. An additional group of males received 5000 ppm. These dose levels were equivalent to 0, 0.44, 4.4, 43.8, 108.3 and 225.2 mg/kg/day in males and 0, 0.56, 5.6, 56.3 and 138.6 mg/kg/day in females, respectively. For chronic toxicity, the NOEL was 108.3 mg/kg/day in males and 56.3 mg/kg/day in females and the LOEL was 225.2 mg/kg/day in males and 138.6 mg/kg/day in females based on marginal decreases in body weight gains.

Discussion of Tumor Data: **There was no evidence of carcinogenicity**.

Adequacy of the Dose Levels Tested: The dose levels tested in this study were based on the results of a range finding study. Based on the body weight gain reductions observed, the dose levels tested were judged to be adequate to assess the carcinogenic potential of halosulfuron-methyl in male and female rats

2. Carcinogenicity Study-Mice §83-2b

MRID No. 42661419

Executive Summary: Groups of male and female CD-1 mice were fed halosulfuron-methyl (98.5%) at 0,30, 300, 3000 or 7000 ppm for 78 weeks. These dose levels were equivalent to 0, 4.0, 41.1, 410 or 971.9 mg/kg/day in males and 0, 5.2, 51, 509.1 or 1214.6 mg/kg/day in females, respectively. For chronic toxicity, the NOEL was 410 mg/kg/day in males and 1214.6 mg/kg/day in females and the LOEL was 971.9 mg/kg/day in males and 1214.65 mg/kg/day in females.

Discussion of Tumor Data: **There was no evidence of carcinogenicity.**

Adequacy of the Dose Levels Tested:. The high dose level tested was the Limit-Dose (7000 ppm) for carcinogenicity testing in this species.

3. Classification of Carcinogenic Potential:

At the September 23, 1993 meeting the HED RfD/Peer review classified halosulfuron-methyl (tentatively) as a **"Group E"** chemical based on the lack of evidence of carcinogenicity in male and female mice as well as in male and female rats..

The HIARC also classified Halosulfuron melthyl as a **"not likely"** human carcinogen according to EPA *Proposed Guidelines for Carcinogen Risk Assessment* (April 10, 1996).

## IV. FQPA CONSIDERATIONS

1. Neurotoxicity Data

Acute and subchronic neurotoxicity studies are not required for halosulfuron-methyl. No evidence of neurotoxicity was observed in the studies available in the toxicology data base. However, in the developmental toxicity study in rats, there was evidence of alterations to the development of the fetal nervous system at the highest dose tested (750 mg/kg/day), including dilation of the lateral ventricles (16 fetuses/5 litters), dilation of the third ventricle (1/1), spinal cord agenesis (1/1), and adrenal agenesis (1/1) at the high dose, and malformed brain cortex (1/1) at the mid dose.

2. Determination of Susceptibility

The data provided no indication of increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure to halosulfuron-methyl. In the prenatal developmental toxicity studies in rats and rabbits and the two-generation reproduction study in rats, effects in the offspring were observed only at or above treatment levels which resulted in evidence of parental toxicity. There is no assessment of potential susceptibility in the area of functional development.

(i) Developmental Toxicity:

In a prenatal developmental toxicity study, pregnant Sprague-Dawley rats (25/dose) received oral (gavage) administration of halosulfuron-methyl (98.5%) in aqueous carboxymethylcellulose and Tween 80 at dose levels of 0, 75, 250, or 750 mg/kg/day during gestation days 6 through 15. For maternal toxicity, the NOEL was 250 mg/kg/day and the LOEL was 750 mg/kg/day based on increased incidence of clinical observations (primarily alopecia and urine stains) and reduced body weight gains, food consumption, and food efficiency. For developmental toxicity, the NOEL was 250 mg/kg/day and the LOEL was 750 mg/kg/day based on decreased mean litter size, increased number of resorptions (total and per litter), significantly decreased mean fetal body weight, and increases in fetal and litter incidences of soft tissue (primarily dilation of the lateral ventricles and other anomalies in the development of the fetal nervous system) and skeletal variations (anomalies or delays in ossification in the thoracic vertebrae, sternebrae, and ribs) (MRID No. 42139425). The Committee noted that both the fetal and litter incidences of dilated lateral ventricles of the brain were statistically significant, and appeared to be dose related, since the finding was also observed at the mid-dose in 2 fetuses of 2 litters. Due to the lack of historical control data, it was not possible to evaluate the biological significance of the low incidence of this finding at the mid-dose level. Therefore, the Committee recommended that the study developmental NOEL and LOEL, as defined by the DER not be revised at this time.

In a prenatal developmental toxicity study with a metabolite, MON 7583, no evidence of maternal or developmental toxicity was seen following oral (gavage) administration at doses of 0, 30, 300 or 1000 mg/kg/day during gestation days 6 through 15. For maternal and developmental toxicity, the NOEL was ≥1000 mg/kg/day, the Limit Dose (MRID No. 43621901).

The prenatal developmental toxicity study in rabbits is discussed in Section II. A. Acute Dietary. For maternal and developmental toxicity, the NOEL was 50 mg/kg/day and the LOEL was 150 mg/kg/day (MRID No. 42139426).

(ii) Reproductive Toxicity:

In a two-generation reproduction study, Sprague-Dawley rats were fed diets containing halosulfuron-methyl (95.9%) at 0, 100, 800 or 3600 ppm for two generations. These dose levels were equivalent to: 0, 6.3, 50.4 or 223.2 mg/kg/day for males and 0; 7.4, 58.7 or 261.4 mg/kg/day for females, respectively. For parental systemic toxicity, the NOEL was 50.5/58.7 mg/kg/day in males/females and the LOEL was 223.2/261.4 mg/kg/day in males/females. The DER states that "equivocal" body weight decrements were observed in pups of both generations. For offspring toxicity, the reviewer established a NOEL of ≥3600 ppm (HDT). This was assessed and confirmed by the previous RfD committee meeting. It was noted by the HIARC that significant decreases in pup body weight were observed from days 7 through 21 in both sexes in the first generation at both 800 and 3600 ppm; the effects at 800 ppm appear to be equivocal, since they were not repeated in the second generation. However, Day 0 decreases in both litters of the second generation were a consistent response. It was noted that the test substance intake for the second generation was actually higher, and the observation of effects not observed in the first generation may have been attributed to that finding. Nevertheless, the lack of late lactation body weight decrements in pups in either litter of the second generation appears to confirm the equivocal nature of the findings observed in the first generation. Due to a lack of definitive information that might further elucidate the equivocal nature of the results, and since the full determination of this issue will have no bearing on uncertainties regarding the toxicity profile or susceptibility issues of this chemical in relation to infants and children, the Committee decided to accept the conclusions as stated in the DER and reevaluated by the previous RfD Committee. (40089316).

3. Recommendation for a Developmental Neurotoxicity Study

Based on the following weight-of-the-evidence considerations, the HIARC determined that a developmental neurotoxicity study in rats **is required** for halosulfuron methyl.

(i) Evidence that support requiring a developmental neurotoxicity study:

- In the developmental toxicity study in rats, there was evidence of alterations to the development of the fetal nervous system at the highest dose tested (750 mg/kg/day), including dilation of the lateral ventricles (16 fetuses /5 litters), dilation of the third ventricle (1/1), spinal cord agenesis (1/1), and adrenal agenesis (1/1) at the high dose, and malformed brain cortex (1/1) at the mid dose.

(ii) Evidence that do not support asking for a developmental neurotoxicity study:

- In the developmental toxicity study in rabbits, there was no evidence of alterations to the developing fetal nervous system.

- There is no evidence of clinical signs of neurotoxicity, brain weight changes, or neuropathology in the subchronic or chronic studies in rats, mice, and dogs.

(iii) Unknown factors:

- There was no evaluation of perfused nervous system tissues, since acute and subchronic neurotoxicity studies in rats were not required.

The HIARC noted that the previous RfD Committee had decided not to require a developmental neurotoxicity study, based upon the likelihood that exposure to this chemical would not attain levels sufficient to observe the observations noted at 750 mg/kg/day in the rat developmental study. The HIARC discussed this aspect and concluded that exposure should not have a bearing on the determination of the need for the developmental neurotoxicity study, but that the decision would be purely hazard-based. Further consideration of the issue of exposure, in relation to the issue of potential effects on functional development, should be performed during risk characterization. The primary concern expressed by the Committee was in regard to the lack of information available in the data base that would allow the determination of whether functional deficits would be observed at dose levels below those which result in frank malformations of the central nervous system. Therefore, HIARC decided, based upon Agency criteria that mandate that a developmental neurotoxicity be required when malformations of the developing nervous system are observed, that this study be required.

4. Determination of the FQPA Factor:

The application of an FQPA factor to ensure the protection of infants and children from exposure to halosulfuron methyl, as required by FQPA, will be determined during risk characterization.

## VI. DATA GAPS

There are no data gaps for the standard Subdivision F Guideline requirements for a food-use chemical by 40 CFR Part 158. However, the Committee determined that based upon the data from the developmental toxicity study in rats, a developmental neurotoxicity study with halosulfuron-methyl is required; therefore, there are significant uncertainties in the assessment of functional development following pre- and/or postnatal exposure to Halosulfuron-methyl.

## VII SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

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

| EXPOSURE SCENARIO | DOSE (mg/kg/day) | ENDPOINT | STUDY |
|---|---|---|---|
| Acute Dietary<br><br>Female 13+, Infants and Children | NOEL=50 | Decreased mean litter size, increased resorptions and increased postimplanation loss | Developmental-Rabbit |
| | **Acute RfD = 0.5 mg/kg/day** | | |
| Acute Dietary Adult Male | None | No appropriate endpoint was available | |
| Chronic Dietary | NOEL=10 | Decrease in bodyweight gain and alterations in hematology and clinical chemistry parameters. | Chronic Toxicity -Dog |
| | | **Chronic RfD = 0.1 mg/kg/day** | |
| Short-Term (Dermal)[a] | Oral NOEL=50 | Decreased mean litter size, increased resorptions and increased postimplanation loss. | Developmental-Rabbit |
| Intermediate-Term (Dermal)[a] | Oral NOEL=10 | Decrease in body weight gain during weeks 0-13. | Chronic Toxicity -Dog |
| Long-Term (Dermal)[a] | Oral NOEL=10 | Decrease in bodyweight gain and alterations in hematology and clinical chemistry parameters. | Chronic Toxicity -Dog |
| Inhalation (Any Time Period) | None | Low toxicity and use pattern does not indicate a need for risk assessment via this route. | |

a = A dermal absorption factor of 75% should be used for these risk assessments.