13544

129009 0021100 021998 TX012501 R001198

Chemical:	**Rimsulfuron**
PC Code:	**129009**
HED File Code	***21100 HIARC***
Memo Date:	**02/19/98**
File ID:	**TX012501**
Accession Number:	**412-01-0045**

HED Records Reference Center
11/15/2000

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

012501

EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

DATE: **February 19, 1998**

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: ***RIMSULFURON*** - 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, 2/19/98
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)
and
Mike Metzger, Co-Chairman 2/23/98
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Stephen Dapson, Branch Senior Scientist
Toxicology Branch 2
Health Effects Division (7509C)

PC Code: 129009

On February 12, 1998, the Health Effects Division's Hazard Identification Assessment Review committee evaluated the toxicology data base of Rimsulfuron and selected doses and endpoints for acute dietary as well as occupational and residential exposure risk assessments, re-assessed the Reference Dose (RfD) established for chronic dietary risk assessment and addressed the sensitivity of infants and children as required by the Food Quality Protection Act (FQPA) of 1996. The Committee's conclusions are presented in this report.

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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: Melba Morrow. Data was presented by John Doherty.

Data Presentation: 2/27/98

John Doherty, Ph. D
Toxicologist

Report Preparation:

Jess Rowland, M.S.
Executive Secretary

I. INTRODUCTION

On February 12, 1998, the Health Effects Division's Hazard Identification Assessment Review committee evaluated the toxicology data base of Rimsulfuron and selected doses and endpoints for acute dietary as well as occupational and residential exposure risk assessments, re-assessed the Reference Dose (RfD) established for chronic dietary risk assessment, and addressed the sensitivity of infants and children from exposure to Rimsulfuron as required by the Food Quality Protection Act (FQPA) of 1996. The need for the additional 10 x factor enhanced sensitivity of infants and children from exposure to Rimsulfuron, as required by FQPA, will determined during risk characterization. The Committee's conclusions are presented below.

II. HAZARD IDENTIFICATION

A. Acute Reference Dose (Acute RfD))

Study Selected: None

MRID. Nos. None

Executive Summaries: None

Dose and Endpoint for Risk Assessment: Not Applicable.

Comments about Study and Endpoint: There were no toxicological effects attributable to a single exposure (dose) observed in oral toxicity studies including the developmental toxicity studies in rats and rabbits. Therefore, a dose and endpoint was not selected for this risk assessment.

This risk assessment is **NOT** 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 §83-1

MRID No. 41931643

Executive Summary: In a chronic toxicity study, groups of Beagle dogs (5/sex/dose) were fed diets containing Rimsulfuron 98.8%) at 0, 50, 2,500, or 10,000 ppm for one year. These dose levels were equivalent to approximately 0, 1.6, 81.8, and 342.4 mg/kg/day for males and 0; 1.6, 86.5, and 358.5 mg/kg/day for females respectively. For males, the

NOEL was 1.6 mg/kg/day and the LOEL was 81.8 mg/kg/day. For females, the NOEL was 86.5 mg/kg/day and the LOEL was 358.5 mg/kg/day. For males, the LOEL was based on increased absolute liver and kidney weights and increased incidence of seminiferous tubule degeneration and increased numbers of spermatid giant cells present in epididymides. For females, the LOEL was based on decreased mean body weight and body weight gain, increased serum cholesterol levels and alkaline phosphatase activity, increased absolute liver weight, and increased relative liver and kidney weights.

Dose/Endpoint for establishing the RfD: NOEL=81.8 mg/kg/day based on statistically significant increases in liver and kidney weights at 342.4 mg/kg/day (LOEL).

Comments about Study and Endpoint: The Data Evaluation Record (DER) established a NOEL of 1.6 mg/kg/day in males. The Committee, however, determined that the increases in kidney and liver weights in males only at the next dose (81.8 mg/kg/day) was of questionable biological significance since the increases showed statistical significance only for the absolute values and not for relative and also there were no corroborative histopathological lesions in the liver or kidneys at this dose. Histopathological lesions at 81.8 mg/kg/day in males in the seminiferous tubules were characterized as unilateral degeneration (2/5) and in the epididymides as spermatid giant cells (3/5) compared to 0/5 (for each lesion) in the controls. The seminiferous tubule lesion was not considered to be toxicologically significant since the occurrence was unilateral and there was no dose-response. The epididymidal lesions were also not considered to be toxicologically significant since they are often associated with infection and/or old age. Consequently, the Committee determined that this dose (81.8 mg/kg/day) based on these effects is not suitable for risk assessment purposes. The committee, therefore, selected the dose of 81.8 mg/kg/day to be the NOEL only for risk assessment purposes. The Committee also determined that the NOEL/LOEL indicated in the DER need not be changed at this time.

In addition, the dog was shown to be the most sensitive species for Rimsulfuron-induced toxicity among subchronic and chronic studies. In subchronic toxicity studies the NOEL/LOEL of 6.25/125 mg/kg/day in dogs was lower than the NOEL/LOEL of 75/375 mg/kg/day in rats. Also, the NOEL of 81.8 mg/kg/day used for risk assessment purposes is still lower than the NOEL of 165 mg/kg/day established for parental systemic toxicity study in the two generation reproduction study. The Committee also concluded that a NOEL of 1.6 mg/kg/day is not supported by the toxicity observed in any of the other studies in the database.

Uncertainty Factor (UF): 100 (10 for inter-species and 10 for intra-species variations) .

$$\textbf{Revised RfD} = \frac{81.8 \text{ mg/kg/day (NOEL)}}{100 \text{ (UF)}} = \textbf{0.818 mg/kg/day}$$

C. Occupational/Residential Exposure

1. Dermal Absorption

No dermal absorption studies are not available. A dermal absorption factor is not applicable, since dermal risk assessments are not required.

Dermal Absorption Factor: Not Applicable.

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

Study Selected: None

MRID No. None

Executive Summary: None

Dose and Endpoint for Risk Assessment: Not Applicable.

Comments about Study and Endpoint: The toxicity profile of Rimsulfuron indicated that there are no toxicological concerns based on the low toxicity observed in studies conducted in mice, rats, rabbits and dogs. The NOELs and LOELs are tabulated below:

Study/Species	NOEL (mg/kg/day)	LOEL (mg/kg/day)
90-Day-Dog	9.63 (M) 10.6 (F)	193 (M) 189 (F)
90-Day-Rat	102 (M) 120 (F)	495 (M) 615 (F)
1-Year-Dog (as determined by the Committee)	81.8 (M) 86.5 (F)	342.4 (M) 358.5 (F)
Developmental-Rabbit	170	500
Developmental-Rat	6000	Not Established
Two-Gen. Report-Rat	175	830
Carcinogenicity-Mouse	351 (M) 488 (F)	1127 (M) 1505 (F)
Carcinogenicity-Rat	11.8 (M) 163 (F)	121 (M) 568 (F)

Thus, the low toxicity, the use pattern (2 oz a.i/acre or 0.125 lbs a.i/acre) and the number of applications (2/year) does not indicate a concern for potential risk. **Based on these factors the HIARC determined that dermal risk assessments are not required.**

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

Study Selected: None

MRID No. None

Executive Summary: None

Dose and Endpoint for Risk Assessment: Not Applicable.

Comments about Study and Endpoint: See Short-Term

This risk assessment is **NOT** required.

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

Study Selected: None

MRID No. None

Executive Summary: None

Dose and Endpoint for Risk Assessment: Not Applicable.

Comments about Study and Endpoint: See Short-Term

This risk assessment is **NOT** required.

5. Inhalation Exposure (Any-Time period)

Except for an acute inhalation toxicity study, there are no other inhalation toxicity studies are available for use in selecting the dose and endpoint for this risk assessment. However, based on the formulation of the product (dry flowable granule containing 25% a.i), the application rate (0.125 lbs a.i/acre), the application method (sprinkler irrigation) and the low acute toxicity (LC_{50}->5 mg/L, Tox. Cat. IV), there is minimal concern for potential inhalation exposure/risk for the proposed use.

This risk assessment is **NOT** required.

D. Margin of Exposure for Occupational/Residential Exposures:

Due to the lack of a toxicological endpoint of concern, Margins of Exposures (MOEs) are not applicable for Occupational/Residential risk assessments.

E. Recommendation for Aggregate Exposure Risk Assessments

Not required; there are no registered residential uses and an acute dietary risk assessment is not required.

III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

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

MRID No: 42047701

Executive Summary: In a combined chronic feeding/carcinogenicity study, male and female Crl:CD BR rats were fed diets containing Rimsulfuron (98.8%) at 0, 25, 300, 3000 or 10,000 ppm for 104 weeks. These dose levels were equivalent to 0, 1.0, 11.8, 121 or 414 mg/kg/day in males and 0, 1.4, 17.1, 163 or 569 mg/kg/day in females, respectively. For chronic toxicity, the NOEL was 11.8 mg/kg/day in males and 163 mg/kg/day in females and the LOEL was 121 mg/kg/day in males and 569 mg/kg/day in females based on decreased body weight gain and increased liver weights.

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

Adequacy of the Dose Levels Tested: Based on the decreases in body weight gain and increases in liver weights observed, the dose levels tested were judged to be adequate to assess the carcinogenic potential of Rimsulfuron in male and female rats.

2. Carcinogenicity Study- Mice §83-2b

MRID No: 41931642

Executive Summary In a carcinogenicity study, male and female Crl:CD-1 (ICR) mice were fed Rimsulfuron (98.8%) at 0, 25, 250, 2500 or 7500 ppm for 18 months. These dose levels were equivalent to 0, 3.5, 35.5, 351 or 1127 mg/kg/day in males and 0, 5, 50.5, 488 or 1505 mg/kg/day in females, respectively. For chronic toxicity, the NOEL was 351 mg/kg/day in males and 488 mg/kg/day in females and the LOEL was 1127 mg/kg/day in males and 1505 mg/kg/day in females based on decreased body weight gain (both sexes), and stomach (females) and testicular (males) lesions.

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

Adequacy of the Dose Levels Tested: Based on the body weight gain reductions and histopathological lesions observed, the dose levels tested were judged to be adequate to assess the carcinogenic potential of Rimsulfuron in male and female mice.

3. Classification of Carcinogenic Potential:

At the July 29, 1993 meeting the HED RfD/Peer review classified Rimsulfuron (tentatively) as a **"Group E"** chemical. This "tentative" classification was based on the lack of evidence of carcinogenicity in mice and rats. However, the Committee concluded that the "final" classification could not be made until the summary of tumor incidences (sic) of each tumor was evaluated.

The HIARC classified Rimsulfuron as a **"not likely"** human carcinogen according to EPA *Proposed Guidelines for Carcinogen Risk Assessment* (April 10, 1996). The HIARC also repeated the previous request for confirmation of the tumor incidences in the rat study by re-evaluation of the tumor data.

IV. MUTAGENICITY

A total of six mutagenicity/genetic toxicity studies evaluated the mutagenic potential of Rimsulfuron for point mutation, ehromosome aberration or other mechanism of genetic toxicity. Rimsulfuron did not cause point mutations in the *Salmonella* (Ames test) strains or gene mutations in CHO cells or chromosome aberrations in human erythrocytes *in vitro* in the presence of absence of metabolic activation. Rimsulfuron also did not cause unscheduled DNA repair or DNA damage in rat primary hepatocytes *in vitro.* In mouse micronucleus studies *in vivo,* there was no evidence of polychromated micronucleated cells in bone marrow at dose levels as high as 5000 mg/kg by gavage. Thus, there is no mutagenicity/genetic toxicity of concern for somatic cells (MRID Nos.;41931622 411356327; 41356328; 41356329;41356330; 42471310).

V. FQPA CONSIDERATIONS

1. Neurotoxicity Data

Acute and subchronic neurotoxicity studies are not required for Rimsulfuron. No evidence of neurotoxicity was observed in the studies available in the toxicology data base.

2. Determination of Susceptibility

The data provided no indication of increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure to Rimsulfuron. 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.

(I) Developmental Toxicity:

In a prenatal developmental study, pregnant rats were given Rimsulfuron (98.8 %) by gavage at dose levels of 0, 200, 700, 2000 or 6000 mg/kg/day during gestation days 7 through 16. For maternal toxicity, the NOEL was 6000 mg/kg/day, the highest dose tested; a LOEL was not established. For developmental toxicity, the NOEL was 6000 mg/kg/day (HDT); a LOEL was not established (MRID No. 41356324).

In a prenatal developmental toxicity study, pregnant New Zealand White rabbits received Rimsulfuron (98.8 %) by gavage at dose levels of 0, 25, 170, 500, or 1500 mg/kg/day during gestation days 7 through 19. For maternal toxicity, the NOEL was 170 mg/kg/day and the LOEL was 500 mg/kg/day based on mortality, abortion and decreased body weight. For developmental toxicity, the NOEL was 500 mg/kg/day and the LOEL was 1500 mg/kg/day since there were only 2 viable pups at 1500 mg/kg/day. Since there was no indication of developmental toxicity at 500 mg/kg/day, a dose causing at least one death, and 2 abortions and reduced body weight gain in the does there is no evidence that the neonates or developing rabbit pups are more sensitive than the does. The study, however, does have a problem. Rimsulfuron was so toxic at 1500 mg/kg/day such that there were 15 deaths among the does and only 2 viable pups in the surviving doe. Although there were 2 abortions in the 500 mg/kg/day dose group, there was no increase in resorptions. Body weight in the pups in the 500 mg/kg/day dose group was not reported to be affected by treatment indicating that the abortions were a maternal effect rather than a direct effect on the pups (MRID No. 41356325).

(ii) Reproductive Toxicity:

In a two-generation reproduction study, Crl:CD-BR rats were fed diets containing Rimsulfuron (98.8%) at 0, 50, 3000 or 15,000 ppm for two generations. These dose levels were equivalent to: 0, 2.8, 165 or 830 mg/kg/day for F_0 males; 0; 3.4, 204 or 1021 mg/kg/day for F_0 females; 0, 3.7, 217 or 1316 mg/kg/day for F_1 males; and 0, 4.3, 264 or 1316 mg/kg/day for F_1 females, respectively. For parental systemic toxicity, the NOEL was 165 mg/kg/day and the LOEL was 830 mg/kg/day based on decreased body weight and body weight gains. For offspring toxicity, the NOEL was 165 mg/kg/day and the LOEL was 830 mg/kg/day based on an increase in the number of pups with "small body size" and decreased pup weight. Decreased weight was also the key finding for systemic effects. Thus, the effect in pups occurred at the same dose level as the systemic maternal effects. (MRID No. 41931644).

3. Recommendation for a Developmental Neurotoxicity Study

Neither the subchronic or chronic toxicity studies in rats and dogs or the developmental toxicity studies in rats or rabbits indicated that the nervous system was specifically affected by treatment with Rimsulfuron. Thus, there is no indication that Rimsulfuron is a neurotoxic herbicide.

There are no series §81-8 (acute) and §82-7 (subchronic) neurotoxicity studies available. It is noted that the rat developmental toxicity study demonstrated a NOEL $\geq$ 6000 mg/kg/day. It is also noted that the dog and rabbit are more sensitive species than the rat based on the subchronic and chronic feeding and developmental toxicity studies. Additionally, owing to the lack of toxicity in the *rat*, the Committee dose not recommend a developmental neurotoxicity study in rat.

4. Determination of the FQPA Factor:

The need for the additional 10 x factor to ensure the safety of infants and children from exposure to Rimsulfuron, as required by FQPA, will 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.

VII SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

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

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY	MOE REQUIRED
Acute Dietary	None	No appropriate endpoint available; risk assessment not required		
Chronic Dietary	NOEL=81.8	Increases in liver and kidney weights.	Chronic Toxicity -Dog	100
		Revised RfD = 0.818 mg/kg/day		
Short-Term (Dermal)	None	No appropriate endpoint available; use pattern does not indicate a need for this risk assessment		
Intermediate-Term (Dermal)	None	No appropriate endpoint available; use pattern does not indicate a need for this risk assessment		
Long-Term (Dermal)	None	No appropriate endpoint available; use pattern does not indicate a need for this risk assessment		
Inhalation (Any Time Period)	None	The low toxicity, use pattern and application method and rate do not indicate a need for risk assessment via this route.		