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

JAN 31 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: RfD/Peer Review Report of MON 12000 (Halosulfuron Methyl)

CASRN. 100784-20-1
EPA Chem. Code: 128721
Caswell No. 957

FROM: George Z. Ghali, Ph.D. G Ghali
Manager, RfD/Peer Review Committee
Health Effects Division (H7509C)

TO: Joanne Miller, PM 14
Fungicide-Herbicide Branch
Registration Division (H7505C)

The Health Effects Division RfD/Peer Review Committee met on September 23, 1993 to discuss and evaluate the toxicology data submitted in support of MON 12000 (Halosulfuron Methyl) registration and to assess a Reference Dose (RfD) for this chemical.

The Committee recommended that an RfD be established based on a no-observable effect level (NOEL) of 10 mg/kg/day for decreased body weight gain and changes in hematological and blood chemistry parameters observed at 40 mg/kg/day in a chronic (one-year) feeding study in dogs. An uncertainty factor (UF) of 100 was used to account for inter-species extrapolation and intra-species variability. On this basis the **RfD** was calculated to be **0.1 mg/kg/day**. It should be noted that no regulatory value was ever established for this chemical by the World Health Organization (WHO) up to this date.

The Committee considered the chronic toxicity studies in rats **(83-1a)** and dogs **(83-1b)**, the carcinogenicity studies in rats and mice **(83-2a and -2b)**, the developmental toxicity studies in rats and rabbits **(83-3a and -3b)** and the reproductive toxicity in rats **(83-4)** to be acceptable. Except for minor revisions, the data evaluation records for these studies were considered to be adequate.

The need for a developmental neurotoxicity study was considered by the Committee based on increase in dilatation of the third ventricle of the brain along with malformation of brain cortex observed in the rat developmental toxicity study. However, it was concluded that under the current use of this chemical, the level of exposure would not warrant such a study.

The high dose level tested in rats was considered adequate for carcinogenicity testing in this strain of rats based upon body weight gain reduction. The dose levels tested in this carcinogenicity study was based on the results of a range finding study. The high dose level tested in the mouse study was a limit dose. The treatment did not alter the spontaneous tumor profile in these strains of rats and mice under the testing conditions. The chemical was, therefore, classified as a **"Group E"** carcinogen.

A. Individuals in Attendance

1. Peer Review Committee Members and Associates (Signature indicates concurrence with the peer review unless otherwise stated).

Reto Engler

Marcia Van Gemert

Karl Baetcke

Henry Spencer

James Rowe

David Anderson

John Tice

George Ghali

Rick Whiting

2. Peer Review Committee Members in absentia (Signature indicates concurrence with the peer review unless otherwise stated).

William Burnam

William Sette

3. Scientific Reviewer(s) (Committee or non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report).

Mike Ioannou

Virginia Dobozy

4. Others:

K. Dearfield, A. Protzel, L. Hansen, L. Kutney and V. Dobozy of HED as observers

CC: Penny Fenner-Crisp
Richard Schmitt
Kerry Dearfield
Marcia Van Gemert
Mike Ioannou
Virginia Dobozy
James Kariya
RfD File
Caswell File

B. Material Reviewed

Material available for review included data evaluation records for a long-term toxicity study in dogs **(83-1a)**, a chronic toxicity/carcinogenicity study in rats **(83-5 or 83-1b and -2a)**, a carcinogenicity study in mice **(83-2b)**, developmental toxicity studies in rats and rabbits **(83-3a and -3b)** and a reproductive toxicity study in rats **(83-4)**, an RfD summary document and a tox. one-liner. The Committee focused the discussion on the following studies.

1. Moore, M. (1992). Combined chronic toxicity study and oncogenicity study in rats with NC-319. MRID No. 42661418, HED Doc. 000000.

Core Classification: Core-minimum data.

Committee's Conclusions and Recommendations:

The chemical was tested in Crl:CD BR rats at 10, 100, 1000 and 2500 ppm (equivalent to 0.44, 4.4, 43.8, 108.3 mg/kg/day in males and 0.56, 5.6, 56.3 and 138.6 mg/kg/day in females). An additional group of males received 5000 ppm (225.2 mg/kg/day). The NOEL/LOEL were considered to be 1000 and 2500 ppm in females and 2500 and 5000 ppm in males based on marginal decrease in body weight gain. At necropsy, the only significant finding was an increase in the incidence of atrophy of the seminal vesicles in the 5000 ppm males. The high dose tested was considered to be adequate for carcinogenicity testing in this strain of rats. The dose selection was based on the results of a range finding study. The treatment did not alter the spontaneous tumor profile for this strain of rats under the testing conditions. The Committee agreed with the reviewer's evaluation and interpretation of data and classification of the study. The study was considered to be acceptable and the data evaluation record was considered to be adequate. This study satisfies data requirement 83-1a and 83-2a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity and carcinogenicity testing in rats.

2. Moore, M. (1992). Oncogenicity study in mice with NC-319. MRID No. 42661419, HED Doc. 000000.

Core Classification: Core-minimum data.

Committee's Conclusions and Recommendations:

The chemical was tested in CD-1 mice at 30, 300, 3000 and 7000 ppm (equivalent to 4, 41.1, 410 and 971.9 mg/kg/day in males and 5.2, 51, 509.1, 1214.6 mg/kg/day in females). The NOEL/LOEL were considered to be 410 and 971.9 mg/kg/day in males based on significant decrease in body weight gain. The NOEL was considered to be 1214.6 mg/kg/day, the highest dose tested in females. At

necropsy, the only significant finding was an increase in the incidence of mineralization in testis and epididymis of males of the high dose group. The high dose tested was considered to be adequate for carcinogenicity testing based on body weight gain decrease in males. The high dose was considered a limit dose for both males and females. The treatment did not alter the spontaneous tumor profile for this strain of mouse under the testing conditions. The Committee agreed with the reviewer's evaluation and interpretation of data and classification of the study. The study was considered to be acceptable and the data evaluation record was considered to be adequate. This study satisfies data requirement 83-2b of Subpart F of the Pesticide Assessment Guideline for carcinogenicity testing in mice.

3. Osheroff, M. R. (1991). Chronic toxicity study in dogs with NC-319 MRID No. 423696211, HED Doc. 009800.

Core Classification: Core-minimum data.

Committee's Conclusions and Recommendations:

The chemical was tested in beagle dogs for one year at 0.25, 1.0, 10.0 and 40.0 mg/kg/day. The NOEL/LOEL were considered to be 1 and 10 ppm in males based on decreased body weight gain and changes in hematology and serum chemistry. The NOEL/LOEL were considered to be 10 and 40 mg/kg/day for females based on decreased overall weight gain and hematological changes. The Committee generally agreed with the reviewer's evaluation and interpretation of data and classification of the study. However, the Committee determined that the decrease in cholesterol level without changes in other clinical parameters is of no toxicological significance. Therefore, the Committee recommended to increase the NOEL/LOEL for males to 10 and 40 mg/kg/day. The study was considered to be acceptable and the data evaluation record was considered to be adequate. This study satisfies data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs.

4. Morseth, S. L. (1990). Rat teratology study with NC-319. MRID No. 42139425, HED Doc. 009483.

Core Classification: Guideline data.

Committee's Conclusions and Recommendations:

The chemical was tested in Crl:CD BR rats at 75, 250 and 750 mg/kg/day. Maternal NOEL/LOEL were considered to be 250 and 750 mg/kg/day based on increased incidence of clinical observations, reduced body weight gains and reduced food consumption and food efficiency. Developmental toxicity NOEL/LOEL were considered to be 250 and 750 mg/kg/day based on decreased mean litter size, increased number of resorptions per dam, increased post-

implantation loss, decreased mean fetal body weight along with increases in fetal and litter incidences of soft tissue and skeletal variations. The Committee generally agreed with the reviewer's evaluation and interpretation of data and classification of the study. The study was considered to be acceptable and the data evaluation record was considered to be adequate. This study satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

5. Morseth, S. L. (1990). NC-319: Rabbit teratology study. MRID No. 42139426, HED Doc. 009483.

Core Classification: Core-minimum data.

Committee's Conclusions and Recommendations:

The chemical was tested in New Zealand white rabbits at 15, 50 and 150 mg/kg/day. Maternal NOEL/LOEL were considered to be 50 and 150 mg/kg/day based on reduced body weight gain and reduced food consumption and food efficiency. Developmental toxicity NOEL/LOEL were considered to be 50 and 150 mg/kg/day based on decreased mean litter size, increased number of total resorptions and resorptions per dam and increased post-implantation loss. The Committee generally agreed with the reviewer's evaluation and interpretation of data and classification of the study. The study was considered to be acceptable and the data evaluation record was considered to be adequate. This study satisfies data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.

5. Lemen, J. K. (1991). Two-generation reproduction study in rats with NC-319. MRID No. 42139427, HED Doc. 009483.

Core Classification: Core-minimum data.

Committee's Conclusions and Recommendations:

The chemical was tested in Crl:CD BR rats at 100, 800 and 3600 ppm (equivalent to 6.3, 50.4 and 223.2 mg/kg/day for males and 7.4, 58.7 and 261.4 mg/kg/day for females). Systemic NOEL/LOEL were considered to be 800 and 3600 ppm based on decreased body weight and reduced body weight gain and reduced food consumption during the pre-mating period. Reproductive toxicity NOEL was considered to be 3600 ppm, the highest dose tested. According to the DER, only equivocal effects were noted in body weight of the offspring at the highest dose tested. The Committee generally agreed with the reviewer's evaluation and interpretation of data and classification of the study. However, the Committee recommended that the systemic and reproductive toxicity NOEL be combined and expressed as systemic/reproductive toxicity NOEL based upon statistically significant depression in pup body weights observed at birth in both males and females of F2 A and B litters (page 19

of the DER). This is consistent with the modest but statistically significant depression in dams during gestation in both generations. The table on page 19 of the DER should also indicate this statistical significance along with the correct body weights for F2B females weights recorded earlier on page 15 of the DER. The study was considered to be acceptable and the data evaluation record was considered to be adequate. This study satisfies data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.

C. Conclusions and Recommendations

1. Reference Dose

The Committee recommended that an RfD be established based on a no-observable effect level (NOEL) of 10 mg/kg/day for decreased body weight gain and changes in hematological and blood chemistry parameters observed at 40 mg/kg/day in a chronic (one-year) toxicity study in dogs. An uncertainty factor (UF) of 100 was used to account for inter-species extrapolation and intra-species variability. On this basis the **RfD** was calculated to be **0.1 mg/kg/day.** It should be noted that no regulatory value was ever established for this chemical by the World Health Organization (WHO) up to this date.

2. Data Base

The Committee considered the chronic toxicity studies in rats (83-1a) and dogs (83-1b), the carcinogenicity studies in rats (83-2a) and mice (83-2b), the developmental toxicity studies in rats (83-3a) and rabbits (83-3b) and the reproductive toxicity in rats to be acceptable. The data evaluation records for these two studies were considered to be adequate. Minor revisions were recommended to some of the data evaluation records. The need for a developmental neurotoxicity study was considered by the Committee based on increase in dilatation of the third ventricle of the brain along with malformation of brain cortex observed in the rat developmental toxicity study. However, it was concluded that under the current use of this chemical, the level of exposure would not warrant such a study.

3. Carcinogenicity

The high dose level tested in rats was considered adequate for carcinogenicity in this strain of rats based upon body weight gain reduction. The dose selection was based on the results of a range finding study. The high dose level tested in the mouse study was a limit dose. The treatment did not alter the spontaneous tumor profile in these strains of rats and mice. The chemical was, therefore, classified as a "Group E" carcinogen.