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

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OCT 1 1993

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: NC-319 Technical (synonymous with MON 12000 Technical): Review of four toxicity studies submitted by the registrant in support of registration of the chemical

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CASE: 023929, 023930, 023935, 023936, 284432
MRID NUMBERS: 426614-17 through 426614-20

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and

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Registrant: Monsanto Company

Action Requested: To support the registration of NC-319, review: (1) combined chronic toxicity/carcinogenicity study in rats; (2) carcinogenicity study in mice; (3) 21-day dermal study in rats; (4) mutagenicity study.

RECOMMENDATIONS: Toxicology Branch II finds the four studies acceptable.

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BACKGROUND MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

NC-319 Technical (synonymous with MON 12000) is proposed for both pre-emergence and post-emergence applications for the control of annual broadleaf weeds and nutsedge in corn and milo. [redacted] will be used with NC-319 for pre-emergent applications. Average use rates for pre-and post-emergence in corn and milo are expected to range from 0.032 -0.075 lbs active ingredient per acre. The average expected use rate for the control of yellow and purple nutsedge is 0.25 lb/acre.

Three formulations have been proposed:

(1) A 50% wettable powder (MON 12051) marketed under the trade name Manage® herbicide for use as a turf herbicide.

(2) A 75% extruded granular formulation (MON 12037) marketed under the trade name Permit® herbicide for use as a post-emergent corn herbicide. In the toxicity testing, the 75% extruded granule was tested as the powder MON 12022. The granule is formed by adding water to the powder and then drying.

(3) A 15% extruded granular formulation marketed under the trade name Battalion® herbicide for pre-emergence use in corn. In the toxicity testing, the 15% granule was tested as the powder MON 12041.

DATA SUMMARY

Repeated Dose Dermal Toxicity (21-Day) Study in Rats (82-2) (MRID #: 426614-17)

Technical NC-319 was applied to the shaved skin of male and female rats for 6 hours/day for 21 days at dosages of 0, 10, 100 or 1000 mg/kg/day. There was a decrease in body weight gain in males treated with 1000 mg/kg/day.

The No Observed Effect Level (NOEL) is 100 mg/kg/day in males and ≥ 1000 mg/kg/day in females.

Classification: Minimum

Carcinogenicity Study in Mice (83-2) (MRID #: 426614-19)

Technical NC-319 was administered in the diet to male and female mice at dosages of 0, 30, 300, 3000 and 7000 ppm (limit dose) for 78 weeks. Males in the 7000 ppm group had decreased body weight gains and an increased incidence of microconcretion/ mineralization in the testis and epididymis. There was no evidence that NC-319 was carcinogenic at the dosage levels tested.

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The No Observed Effect Level (NOEL) = males - 3000 ppm (410 mg/kg/day); females - ≥ 7000 ppm (1214.6 mg/kg/day)

The Lowest Observed Effect Level (LEL) = males - 7000 ppm (971.9 mg/kg/day); females - > 7000 ppm (1214.6 mg/kg/day)

The Maximum Tolerated Dose (MTD) = males - 7000 ppm (971.9 mg/kg/day); females - > 7000 ppm (1214.6 mg/kg/day)

Classification: Minimum

Combined Chronic Toxicity/Carcinogenicity Study in Rats (83-5) (MRID #: 426614-18)

Technical NC-319 was administered in the diet to male and female rats for 104 weeks at dosages of 0, 10, 100, 1000 and 2500 ppm. An additional group of males received 5000 ppm. (An agreement between EPA and the sponsor established the dosage levels.) There was a decrease in body weight gain in the males and females in the highest dosage groups. There was no evidence that NC-319 was carcinogenic at the dosage levels tested.

The No Observed Effect Level (NOEL) = males - 2500 ppm (108.3 mg/kg/day); females - 1000 ppm (56.3 mg/kg/day)

The Lowest Observed Effect Level (LEL) = males - 5000 ppm (225.2 mg/kg/day); females - 2500 ppm (138.6 mg/kg/day)

The Maximum Tolerated Dose (MTD) = males - 5000 ppm (225.2 mg/kg/day); females - 2500 ppm (138.6 mg/kg/day)

Classification: Minimum

Mutagenicity: Gene Mutation (HGPRT) in Cultured CHO Cells (84-2) (MRID #: 426614-20)

Technical NC-319 failed to produce mutations at the HGPRT locus in CHO cells treated with the test article at concentrations ranging from 100 to 900 ug/ml in the presence and absence of liver S9.

Classification: Acceptable

Toxicology Profile for NC-319 (MON 12000) (40 CFR 158.340)

A. Data Requirements	Required	Satisfied
Technical		
81-1 Acute oral	yes	yes
81-2 Acute dermal	yes	yes
81-3 Acute inhalation	yes	yes
81-4 Primary eye irritation	yes	yes
81-5 Primary dermal irritation	yes	yes
81-6 Dermal sensitization	yes	yes
82-1 Subchronic feeding (rats)	yes	yes
82-1 Subchronic feeding (dog)	yes	no[1]
82-2 21-Day dermal	yes	yes
82-3 90-Day dermal	no	n/a
82-4 Subchronic inhalation	no	n/a
82-5 21-Day delayed neurotoxicity	no	n/a
83-1 Chronic feeding (rodent)	yes	yes[2]
83-1 Chronic feeding (nonrodent)	yes	yes[2]
83-2 Carcinogenicity (rat)	yes	yes[2]
83-2 Carcinogenicity (mouse)	yes	yes
83-3 Developmental toxicity (rat)	yes	yes
83-3 Developmental toxicity (rabbit)	yes	yes
83-4 Multigeneration reproduction (rat)	yes	yes
83-5 Combined chronic (rat)	yes	yes
84-2(a) Mutagenicity	yes	yes
84-2(b) Mutagenicity	yes	yes
84-4 Mutagenicity	yes	yes
85-1 Metabolism	yes	yes
85-2 Domestic animal safety	no	n/a
85-3 Dermal absorption	no	n/a

Comments

[1] This data requirement is satisfied by an acceptable chronic dog study.

[2] Combined chronic toxicity/carcinogenicity study has been completed.

Formulations [MON 12051 (50% a.i.), MON 12037 (75% a.i.) and MON 12041 (15% a.i.)]

	Required	Satisfied
81-1 Acute Oral Toxicity	yes	yes
81-2 Acute Dermal Toxicity	yes	yes
81-3 Acute Inhalation Toxicity	yes	yes
81-4 Primary Eye Irritation	yes	yes

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81-5 Primary Dermal Irritation	yes	yes
81-6 Dermal Sensitization	yes	yes

B. Toxicology Issues

1. RfD

The RfD/Peer Review Committee will consider the oral RfD for NC-319 (MON 12000) in the near future.

2. Carcinogenicity

There is no evidence that NC-319 (MON 12000) is carcinogenic in the two rodent species tested.

3. Toxicology data gaps

The registrant has satisfied all of the data requirements.

4. Updated, selected one-liners

Attached are updated, selected one-liners to support the data requirements.

5. Labeling Issues

The label for Battalion® has a Warning statement regarding eye injury, however the primary eye irritation study for MON 12041 was classified as Toxicity Category III which would require a Caution statement.

C. Recommendations

Toxicology Branch II has determined that the existing data base for Technical NC-319 (MON 12000) and three formulations is adequate to support the registration of the products.

ADDENDUM TO MEMO ON NC-319

The HED RfD/Peer Review Committee met on September 23, 1993 to discuss NC-319 (MON 12000). It was decided that the No-Observed Effect Level (NOEL) from the chronic dog study (MRID # 423962-11), should be 10 mg/kg/day rather than the original 1 mg/kg/day. This revised NOEL and an uncertainty factor of 100 will be used to calculate the RfD. The reproductive NOEL for the multigeneration reproduction study in the rat (MRID # 421394-27) was also revised from ≥ 3600 ppm to 800 ppm based on statistically significant dpresssion in pup body weights at birth in both males and females of the F_2 A and B litters. It was agreed that there was no evidence from either of the long-term studies in rats and mice that the chemical was carcinogenic in these species.

ADDENDUM TO MRID # 423962-11 (Chronic Oral Toxicity in Dogs with MON 12000)

Based on the recommendation of the Health Effects Division RfD Committee, the systemic NOEL for male dogs in the chronic dog study is changed from 1.0 mg/kg/day to 10.0 mg/kg day, and the systemic LEL for male dogs is changed from 10.0 mg/kg/day to 40.0 mg/kg/day. The systemic LEL is based on decreased body weight gain in male dogs observed at the 40.0 mg/kg/day dose level.