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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

11/26/85

DATE:

SUBJECT: Agency Response To Petitioner's Explanation of Selection Of Doses In COMMAND Rat Teratology Study (FMC Study No. A83-1142)

TO: Robert Taylor, PM #25
Registration Division (TS-767)

FROM: Carolyn Gregorio, Toxicologist CMG
Toxicology Branch/HED (TS-769) 11-25-85

THRU: Clint Skinner, Ph.D. for Thomas Edwards 11-25-85
Section Head,
and
Theodore M. Farber, Ph.D. for CMS 11/26/85
Branch Chief,
Toxicology Branch/HED (TS-769)

Chemical: COMMAND (FMC-57020; Dimethazone)

Caswell No.: 463D

Petitioner: FMC Corporation

EPA Identifying No.: 279-GNLE/ 279-GNLG/ 279-GNLU/ 4F3128

EPA Accession No.: 073828

Action Requested: Respond to the Petitioner's explanation of selection of doses for the previously submitted rat teratology study (FMC Study No. A83-1142, dated June 29, 1985; EPA Accession No. 072829).

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Background: The doses used in the definitive study (FMC Study No. A83-1142) were 0, 100, 300, and 600 mg/kg/day from days 6 though 15 of gestation. Clinical signs of toxicity were transient decreased locomotion and abdominogenital staining which were observed in the 300 and 600 mg/kg/day treatment groups. Body weight weight gains were comparable for treatment and control groups throughout dosing until sacrifice. A 12% decreased mean food consumption was observed in the 600 mg/kg/day dams on days 6 through 13 of gestation when compared to controls.

Mean fetal weights were decreased 7% in the 600 mg/kg/day treatment group when compared to concurrent controls. A statistically significant increase in the "delayed ossification and/or absence" of 4 or more sternebrae was observed in the 300 and 600 mg/kg/day groups when compared to controls.

No teratagenocity was observed in any treatment group or in the control group.

Data Submitted:

1.) FMC 57020 Rat Range-Finding Teratology Study (WIL-91145; FMC A81-652); Conducted by WIL Research Lab for FMC, dated September 24, 1982.

Sprague-Dawley rats were given by gavage 0, 10, 50, 100, 200, or 400 mg/kg/day of COMMAND from gestation day 6 through 15. "There were no signs of toxicity in the 10 mg/kg/day group. Dried red material around nares was observed in the 50, 100, or 200 mg/kg/day groups without any effect on body weight gains. Urogenital staining, dried red material around nares and oral cavity and moderate body weight reduction during treatment were noted in the 400 mg/kg/day group as being attributed to FMC 57020."

2.) FMC 57020 Rat Range-Finding Teratology Study (FMC A83-1142); Conducted by FMC Toxicology Lab, dated June 20, 1985.

Sprague-Dawley rats were given by gavage 0, 400, 475, 550, or 625 mg/kg/day of COMMAND from gestation day 6 through 15. "There were no deaths in any of the test groups. There was no apparent treatment-related effect on either body weight or body weight gain. Food consumption was similiar amoung all dosage groups. Predominant [clinical observations] signs included abdominogenital staining and decreased locomotion. These signs were observed with increasing frequency amoung animals receiving 475, 550, or 625 mg/kg/day. No signs

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were observed in the 400 mg/kg/day or vehicle control groups. There were no treatment-related difference in maternal of fetal parameters observed amoung the groups. Based on the incidence of clinical observations, the recommended dosage levels for the definitive rat teratology study with FMC 57020 Technical (Study No. A83-1142) are 0, 100, 300 and 600 mg/kg/day."

AGENCY RESPONSE TO THE DOSE SELECTION

FMC has stated (letter, Cuirle to Akerman, November 7, 1985) that the doses for this study were based on the following points:

a.) the highest dose (600 mg/kg/day) selected for the study "was almost 1/2 the female LD_{50} (1,369 mg/kg). During the LD_{50} study, the predominant signs of intoxication (other than death) at all doses that were observed were decreased locomotion and abdominogenital staining", and

b.) the same clinical signs of toxicity were observed in the "FMC-conducted pilot" study at both 550 and 625 mg/kg/day doses.

The Toxicology Branch recommends that although the highest dose tested is marginal with respect to maternal toxicity (clinical signs only), the data are sufficient to support the regulatory requirement for a rat teratology study. The body of toxicological data (rat chronic feeding study, rat 2-generation reproduction, rat acute oral) demonstrate that COMMAND has a low toxicity potential.

The Petitioner, however, should be cautioned that in future situations where low toxicity is evidenced in the available toxicology data, there is a "limit test" described in the Agency Guidelines (November, 1982) which is designed to provide adequate data for teratology studies in which compounds of low toxicity are being studied.

Assume this to mean minimum

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