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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

DATE:

SUBJECT: Review of Registrant's Submitted Historical Control
Data For The Rat Teratology Study.

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

FROM: Carolyn Gregorio, Toxicologist *CK*
Toxicology Branch/HED (TS-769) *45*

THRU: Clint Skinner, Ph.D. *Clint Skinner*
Section Head,
and
Theodore M. Farber, Ph.D.
Branch Chief,
Toxicology Branch/HED (TS-769)

Chemical: COMMAND (FMC-57020, Dimethazone)

Caswell No.: 463D

Petition No.: 4F3128; 270-GNLG; 270-GNLU)

Accession No.: 073783

Petitioner: FMC Corporation

Action Requested: Review the historical control data requested
by the Agency (memo, Akerman to FMC, Sept. 15, 1985) to clarify
the Petitioner's submitted rat teratology study (FMC Study No.
A83-1142, June 29, 1984; EPA Acc. No. 072829).

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background: The Petitioner was requested to provide historical control data for Sprague-Dawley rats used in teratology studies conducted at FMC laboratories for the years 1982 through 1984. A statistically significant increase in the incidence of delayed ossification and/or absence of four sternebrae were observed in the mid (300 mg/kg/day) and high (600 mg/kg/day) doses and a non-statistically significant increase of hydronephrosis and hydroureter were observed in all dose groups (100, 300, 600 mg/kg/day) as indications of fetotoxicity. No historical control data were available to provide perspective for these fetotoxic effects. In addition, the lack of any reported teratological finding in this study was considered very unusual, especially since the 2-generation reproduction study (Toxigenics Study No. 450-1095, June 12, 1984) did report several severe teratogenic findings (two fetuses with hind limb abnormalities; one fetus with no anal opening). And therefore, a laboratory data audit was requested (memo, Gregorio to Taylor, August 20, 1985).

Conclusion: The Petitioner has submitted the following data (see Attachment for submitted information):

- 1.) control data for skeletal variations and visceral anomalies for three studies conducted at FMC from September 1983 to present; these three studies included the control data for the study in question (Study # A83-1142) and, control data for one study which is "a draft report which had not been submitted to EPA" (Study # A84-1173) and, control data for another study, in which no other additional information was provided (Study # A83-1091) and,
- 2.) positive control data for skeletal malformations, visceral malformations, and visceral anomalies for aspirin.

The Petitioner submitted historical control data are insufficient to adequately explain the lack of teratogenic findings or provide perspective for the fetotoxic finding of delayed ossification and/or absence of four sternebrae observed in the study.

The data provided do suggest a low spontaneous frequency of malformations in this strain at the FMC laboratory (Table 1). However, due to the small sampling size (three studies) and the large variation within the data, a definitive assessment

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cannot be determined. In addition, the historical control data submitted do not adequately address the fetotoxic effect of the multiple missing sternbrae observed in the study. However, these historical control data will be helpful in concert with the requested Laboratory Data Audit.

Table 1. Selected Skeletal Malformation Parameters For Historical and Positive Controls

Study #	A83-1091	A84-1173	Positive Cont.	A83-1142 ¹
Interparietal - absent	1/144 (0.7%)	0/140 (0%)	16/61 (26.2%)	0/147 (0%)
Pubis - absent	0/144 (0%)	1/140 (0.7%)	4/60 (6.7%)	0/147 (0%)

1/ COMMAND rat teratology study

observed with malformation/total # fetuses observed