



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

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JUN 21 1986

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

DATE:

SUBJECT: Agency Review of Petitioner's Reevaluation Of
COMMAND Rat Teratology Study (FMC Study No. A83-1142)
By Independent Teratologist

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

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

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

Chemical: COMMAND (FMC-57020; Dimethazone)

Caswell No.: 463D

Petitioner: FMC Corporation

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

EPA Accession No.: 260772

Action Requested: Review the Petitioner's reevaluation
of fetal skeletal and visceral specimens 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: In the original review, (Gregorio to Taylor, August 20, 1985), the rat teratology study was classified as Supplementary. The Petitioner was requested to provide historical control data and an explanation of why the doses selected in this study were chosen. In addition, the study was recommended for a Laboratory Data Audit based on "the lack of any reported teratological findings in this study, which [is considered] extremely unusual" especially when several severe teratological findings were observed in the 2-generation rat reproduction study (Toxigenics Study No. 450-1095, June 12, 1984).

The Agency conducted the requested laboratory data audit (conducted by D. Goldman and B. Sonawane of the Office of Compliance Monitoring on October 3 and 4, 1985; report dated November 12, 1985). The Agency auditors recommended that an independent teratologist "reexamine the fetal specimens (skeletal and visceral) using criteria acceptable to the program office [OPP/TB]."

In response to the Agency's recommendation that an independent teratologist reexamine the fetal specimens, the Petitioner contracted Dr. E. Marshall Johnson (Thomas Jefferson University), to serve as an independent teratologist. Dr. Johnson contacted Dr. Mildred Christian (Argus Research Labs) to conduct a "blind" rereading of the fetal specimens and provide a tabulation of findings. Following the rereading of the fetal specimens by Dr. Christian, Dr. Johnson provided his interpretation of the "Argus findings and compar[ed] them to the findings reported by FMC."

Response:

1.) Dr. Mildred Christian's rereading of the fetal specimen's concluded that:

a. the skeletal examination indicated "minor reversible dosage-dependent delays in fetal ossification" which were observed at the 300 and 600 mg/kg/day doses; these were described as "incomplete incomplete or unossified manubrium, incomplete or unossified sternal centra, unossified xiphoid, unossified caudal vertebrae, unossified metacarpals, unossified hindpaw phalanges, (Petitioner's submitted Table 2; attached).

b.) the visceral examination indicated that no noteworthy changes were observed at any treatment level including the FMC reported findings of hydronephrosis and hydro-ureter, about which Dr. Christian stated that "I believe

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their [FMC] findings (hydronephrosis, dilated ureter, convoluted ureter) reflect their small experience in evaluating normal range of development, as we [Argus] did not consider these alterations to be present" (Petitioner's submitted Table 1, attached).

c. no malformations were observed in any group.

2.) Dr. Marshall's evaluation of the entire rat teratology study and interpretation of the Argus reexamination of the fetal specimens concluded that:

"The substance FMC 57020 was evaluated in a standard and uncompromised Segment II-type of safety evaluation in pregnant Sprague-Dawley rats. No congenital abnormalities were produced by this chemical at any dosage. The only differences between the fetuses of treated and control dams were delays of fetal skeletal maturation in dams treated at overtly maternally toxic dose levels. In each evaluation of the fetuses the exposure level of 100 mg FMC 57020/kg/da 6-15 of gestation was a clear no-effect level."

Conclusion: Although some differences in final tabulation of delayed ossification were observed when the reread of the fetal specimens were completed, "the pattern of effects [were] virtually identical to that of the first [FMC] evaluation." Therefore, the data reported by the independent teratologists, Dr. Marshall Johnson and Dr. Mildred Christian, in conjunction with the data provided in the original report are sufficient to satisfy the Agency's concern with regard to the rat teratology study (FMC Study No. A83-1142, June 29, 1984) and the study should be reclassified as MINIMUM.

Maternal toxicity was evidenced by clinical signs of toxicity (decreased locomotion, abdominogenital staining, chromo-rhinorrhea) at 300 (mid-dose) and 600 (high-dose) mg/kg/day.

Fetotoxic treatment-related effects were decreased mean fetal weights (7%) in the 600 mg/kg/day treatment group and delayed ossification observed in the 300 and 600 mg/kg/day groups (incomplete or unossified manubrium, incomplete or unossified sternal centra, unossified xiphoid, unossified caudal vertebrae, unossified metacarpals, unossified hindpaw phalanges). These skeletal alterations are consistent with early generalized disturbances and are considered to be reversible delays as skeletal development is late in prenatal

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life and is not complete for several days after birth.

No fetus had no visceral or skeletal malformation.

Based on the above data, the developmental toxicity no-effect level is 100 mg/kg/day.

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