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

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JAN 17 1986

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

DATE

SUBJECT: Preliminary Assessment Of The Agency Sponsored Data
Audit Of The COMMAND Rat Teratology Study (FMC
Study No. A83-1142)

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

FROM: Carolyn Gregorio, Toxicologist
Toxicology Branch/HED (TS-769) *CHG*
12-30-85

THRU: Clint Skinner, Ph.D.
Section Head, *Clint Skinner*
and
Theodore M. Farber, Ph.D. *1-6-86*
Branch Chief, *John C. B.S.*
Toxicology Branch/HED (TS-769) *1/15/86*

Chemical: COMMAND (FMC-57020; Dimethazone)

Caswell No.: 463D

Petition No.: 4F3128

EPA Record No.: 162393

Petitioner: FMC Corporation

Action Requested: Agency personnel, Dr. Dexter Goldman and
Dr. Babasaheb Sonawane, conducted a data audit of the rat
teratology study (FMC Study No. A83-1142; EPA Accession No.
072829). Their individual comments, with respect to their
findings are attached. In addition FMC has responded to
their comments (letter, Cuirle to Akerman, November 7, 1985)
and is also attached.

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Background: The doses used in the study were 0, 100, 300, and 600 mg/kg/day from days 6 through 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 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 teratogenicity was observed in any treatment group or in the control group.

Agency Audit Questions and Responses: The following observations were identified by the Agency's Auditors and responses were made by FMC:

1.) "The adequacy of the doses selected."

FMC has stated 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 LD₅₀ (1,369 mg/kg). During the LD₅₀ 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 EPA auditors have stated that they "were not convinced that an effective maximum dose had been attained as there was no evidence of maternal toxicity and limited evidence of fetotoxicity."

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

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and in the rat teratology study a low toxicity was observed, as marginal maternal toxicity was demonstrated as evidenced by the clinical signs of toxicity described previously and slight fetotoxicity was observed as evidenced by the lower fetal weights and delayed ossification, also previously described.

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

2.) "The supervision of the technicians by the consultant teratologists and, accordingly, reevaluation of the individual findings."

FMC has stated that: "we were confident in the abilities of the technical supervisor and the technician in charge to adequately conduct teratology studies with the assistance of an independent consultant. She [Nancy Nadasky] was asked to verify any unusual or questionable findings, to aid in the interpretation and classification of findings, to be present the first day of scheduled Cesarean sections in order to verify any external findings noted and to review the final report."

The EPA auditors have recommended that "an independent professional teratologist may be designated to reexamine the fetal specimens (skeletal and viseral)" and cited several reasons for that conclusion:

a.) that "the technicians assigned to the study had adequate training in teratology, but lacked supervision of a professional teratologist" and,

b.) that "no evidence of examination of skeletal specimens by the consultant was available or claimed by the FMC staff. What has been classified as indicators of delayed skeletal ossifications, (e.g., skull bones, thoracic vertebrae, caudal vertebrae, metacarpals, etc.), could be precursors to major malformations" and,

c.) although the training records indicate that the technicians had been examined by the MARTA (Mid-

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Atlantic Reproduction and Teratology Association),
"no evidence was available or claimed for MARTA's
certification of the validity of the results" and,

d.) that the positive control study using aspirin
"was conducted prior to the teratology study under
consideration (FMC-A83-1142) as a practice run for the
technicians."

The Toxicology Branch is in agreement with the EPA auditors
and requests that an independent professional teratologist
should reexamine the skeletal and visceral specimens.

A discussion, with regard to the reexamination of the
skeletal and visceral specimens, was held (December 5,
1985) between Agency personnel (William Burnam, Clint
Skinner, Carolyn Gregorio, Jim Yowell) and FMC personnel
(Martin Fletcher, Director of Toxicology; Eunice Cuirle,
Registration Specialist). FMC indicated that they had
already contacted Dr. Marshal Johnson and requested that
he conduct the company sponsored re-read. The Toxicology
Branch agreed with the selection of Dr. Johnson and will
re-review the study in conjunction with Dr. Marshal's
final report.

3.) "The potential effects of exposure of the pregnant animals
to low temperatures through failure of the heating system."

FMC has stated that: "Although there was a short period of
low temperatures recorded in this study, no adverse
effects due to this incident were observed at the time
of, or following, the incident."

The Toxicology Branch is in agreement that the data
reflect the FMC contention that no uncharacteristic
changes were noted in any of the parameters examined
in the study and since the entire population of animals
in the study were exposed to the same environmental
change, there need not be any further explanation.

4.) "The criteria used for classification of skeletal
malformations."

FMC has made no response to the EPA auditors question with
regard to this question. However, during the recommended
reexamination of the fetuses, the independent professional
teratologist should provide the criteria.

CONCLUSIONS:

1.) The Toxicology Branch has determined that the dosing,
although marginal, is adequate for the purposes of the

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study.

2.) The Toxicology Branch has determined that there was no significant impact on the animals as a result of the temperature alteration experienced for 36 hours.

3.) The Toxicology Branch is in agreement with the Agency auditors and recommends that an independent professional teratologist reexamine all the fetal specimens (skeletal and visceral).

4.) FMC has initiated a company sponsored reexamination of all the skeletal and visceral specimens by Dr. Marshal Johnson. The Toxicology Branch agreed with the selection of Dr. Johnson and will re-review the study in conjunction with Dr. Johnson's final report.

cc: Reto Engler

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