UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

AUG 28 1985

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FMC Corporation
Agricultural Chemical Group
2000 Market Street
Philadelphia, Pennsylvania 19103

Attention: Ms. Eunice M. Cuirle

Dear Ms. Cuirle:

Subject: Command® Technical
EPA File Symbol 279-GNLE
Command® 4EC Herbicide
EPA File Symbol 279-GNLG
Command® 6EC Herbicide
EPA File Symbol 279-GNLU
Pesticide Petition No. 4F3128

We have received the historical control data for the rat teratology study and have assigned it accession number 073783. These data are currently under review. We have completed review of toxicology data submitted in support of registration of the subject products and petition request. Our comments follow:

TOXICOLOGY

2-year Feeding/Onco - Mouse (FMC Study No. A81-651; Toxigenics Stud, No. 410-0817; July 25, 1984). This study has been classified as Supplementary; the Agency has decided, however, that it will support registration for soybean use only. Based on the following, it has been decided that a Maximum Tolerated Dose (MTD) had not been achieved:

1. The absence of body weight change (at least a 10 percent decrement) throughout the study for any treatment group when compared to concurrent controls.

2. The termination of the 4000 and 8000 ppm treatment groups at 3 months without sufficient reasoning that these dose levels would be expected to exceed a MTD for a 24-month study and, thereby, jeapordize the completion of the study.

CONCURRENCES								
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[The study pathologist (August 3, 1985, letter, Harold W. Casey, Louisiana State University, to John R. DeProspo, FMC Corporation) reported that he terminated these doses at 3 months because "absolute enlargement of the liver plus histologic megalocytosis were found at 2000 and 8000 ppm dose levels that were examined microscopically (the 4000 ppm dose groups were not examined miscroscopically). Based on these findings coupled with those found in the previous 28-day study (Toxigenics Study 410-0744 and FMC Study A81-612) showing the liver as the target organ, it appeared that the compound had both a time and dose dependent effect. These data were interpreted to indicate that the survival of mice in the 4000 and 8000 ppm dose levels could be significantly shortening during the course of a 24-month study and, therefore, the recommendation was made that the 2000 ppm dose level should be used as the maximum tolerated dose group."]

3. The absence of any life-threatening or consistent statistically significant changes in any of the examined parameters in any of the treatment groups throughout the 24-month study when compared to concurrent controls.

FMC letter of February 1, 1985, reported that preliminary analysis in Command Technical produced by [redacted] is different than that previously submitted. For this reason, we are currently verifying the quantity and significance of this impurity.

As stated above, the Agency has determined that this study will support registration for soybean use. The study will need to be repeated to support future uses of Command. We will provide specific guidance on this matter when the registration for soybean use is issued.

2-Generation Reproduction - Rat (Toxigenics Study No. 450-1095, June 12, 1984). Decreased body weight, decreased food consumption, increased liver absolute and/or relative to body weight ratio, kidney, and ovary weights were observed in the 2000 and 4000 ppm parents. In addition, an increased incidence of dilated/distended kidneys in the 4000 ppm males and an increased incidence of urine-soaked and/or yellow-brown fur and a decreased fertility index were noted in the 4000 ppm females when compared to concurrent controls.

Slight decreases in the percentage of viable pups/litter, associated with slight increases in the percentage of dead and/or cannibalized pups and a statistically significant

decrease in pup weights were observed at the 2000 and 4000 ppm groups. In addition, one pup in the 1000 ppm dose group and another in the 4000 ppm dose group had severe hind limb abnormalities (non-functional and extended limbs with no flexion at the ankle, respectively) and one pup in the 4000 ppm group had no anal opening. Although these malformations were not statistically significant and were not dose related, causal relationship with the test compound cannot be ruled out.

Parental NOEL = 1000 ppm	Progeny NOEL = 100 ppm
Parental LEL = 2000 ppm	Progeny LEL = 1000 ppm

Teratology - Rat (FMC Study No. A83-1142). This study has been classified as Supplementary. Historical control data, requested as a result of this review, are currently under review. In addition, it will be necessary to provide an explanation of the dose selection used. This additional information is essential for clarification because several severe malformations were observed in the 2-generation rat reproduction study (reported above) at dose levels which were similar to those used in this study.

Maternal toxicity was observed as demonstrated by clinical signs of toxicity (decreased locomotion, abdominogenital straining, chromorhinorrea) at 300 and 600 mg/kg (highest dose tested).

As an indication of fetotoxicity, there was a statistically significant (chi-square) increase in the incidence of delayed ossification or absence of four sternebrae in the 300 and 600 mg/kg groups when compared to concurrent controls. In addition, hydronephrosis and hydroureter were observed more frequently, but not statistically significant, in all dose groups when compared to concurrent controls. No historical control data were available to provide perspective for these fetotoxic effects.

No teratogenic response was observed at any dose. Again, no historical control data were available to provide perspective to these findings.

Metabolism - Rat (PRI Study No. Fm-124r, FMC Study No. PC-0017, March 22, 1984; FMC Study No. P-0898, June 18, 1984). Two metabolism studies were provided which indicate that Command is excreted in the urine and feces (90-99 percent) within 72 hours of treatment for single oral dose (5 mg/kg), single I.V. dose (3 mg/kg), and multiple oral dose (5 mg/kg) for males and females. After a single oral high dose administration (900 mg/kg), excretion was slightly different in that the test compound was excreted in urine the rate of 83 percent and 71

percent for females and males, respectively, over 7 days. The excretion in the feces was 15 percent and 31 percent for females and males, respectively. No tissue retention was observed in any of the studies.

Eighteen metabolic products were identified in the urine and feces over 48 hours.

Mutagenicity. The results of the submitted mutagenicity assays are as follows:

Study Type	Results
Technical (FMC 57020)	
Reverse Mutation - Salmonella (FMC No. A80-403)	Negative (without activation)
Reverse Mutation - Salmonella (Microbiological Assoc. No. A84-1273)	Negative (with/without activation)
Mutagenicity, CHO/HGPRT (Microbiological Assoc. No. A83-1143)	Weakly Positive (without activation)
Mutagenicity, in vivo cytogenetics (Microbiological Assoc. No. A82-778)	Negative
Mutagenicity, Unscheduled DNA Synthesis (Microbiological Assoc. No. A83-1036)	Negative
Intermediate [redacted] INERT INGREDIENT INFORMATION IS NOT INCLUDED	
Mutagenicity, Reverse Mutation (Microbiological Assoc. No. A84-1189)	Positive (with/without activation)
Intermediate [redacted] INERT INGREDIENT INFORMATION IS NOT INCLUDED	
Mutgenicity, Reverse Mutation (Microbiological Assoc. No. A84-1281)	Positive (with/without activation)

Intermediate [redacted] INERT INGREDIENT INFORMATION IS NOT INCLUDED

Mutagenicity, Reverse Mutation (Microbiological Assoc. No. A84-1188)	Positive (with/without activation)
Mutagenicity, Reverse Mutation (Microbiological Assoc. No. A83-1111)	Positive (with/without activation)

A brief summary of all the toxicological data reviewed for technical Command (FMC 57020) is enclosed.

Sincerely yours,

Robert J. Taylor
Product Manager (25)
Fungicide-Herbicide Branch
Registration Division (TS-767C)

Enclosure