KS-6
TXR-5659

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

JAN 12 1987

005659

MEMORANDUM

Subject: Command® : Review of the Data Base of Command®

To: Jim Yowell PM #25
Registration Division (TS-767c)

From: Whang Phang, Ph.D.
Pharmacologist
Toxicology Branch/HED (TS-769c) Whang Phang 1/12/87

Through: Marcia van Gemert, Ph.D. M. van Gemert 1/12/87
Section Head
and
William Burnam, Deputy Branch Chief
Toxicology Branch/HED (TS-769c) W. Burnam 1/12/87

Chemical: Command® (FMC 57020, Dimethazone)

Caswell No.: 463D; EPA ID. No.: 4F3128; Project No. 7-0256

Petitioner: FMC Corp.

Action Requested: To review the toxicology data file of Command®, to determine if the issue of maximum tolerated dose (MTD) in a 2-year mouse feeding/oncogenicity study (FMC Study No. A-81-651, July 25,1984) was resolved, and to consider if the studies would support the use of Command® on additional crops.

Discussion and Conclusion:

1). In examining the data file, there is a memorandum concerning the issue of MTD in the 2-year mouse feeding/oncogenicity study (memo, Gregorio to Yowell, April 18, 1986). According to the memorandum, the Toxicology Branch has utilized a decision tier scheme for addressing the adequacy of chronic studies in which the MTD has not been achieved (draft: Toxicology Branch Position Paper on Maximun Tolerated Dose in Oncogenicity Studies). It has been determine that the study is adequate.

2). This reviewer has discussed the adequacy of this 2-year mouse feeding/oncogenicity study with Mr. William Burnam, Deputy Branch Chief. He confirmed that the study has been considered as adequate. This study is classified Core Minimum.

** 738 187

005659

3). Based upon the previous ADI printout (Attachment). Granting the tolerance of soybeans (0.05 ppm) had used 0.03% of the ADI. Therefore, the studies could support additional crops provided the residue levels in those crops are acceptable.

2

739

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

005659

April 18, 1986

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

DATE:

SUBJECT: Request For "8 Point Summary" For COMMAND

TO: Jim Yowell, PM #25
Registration Division (TS-767)

FROM: Carolyn Gregorio, Toxicologist
Toxicology Branch/HED (TS-769)
1-29-86

THRU: Clint Skinner, Ph.D.
Section Head,
and
Theodore M. Farber, Ph.D.
Branch Chief,
Toxicology Branch/HED (TS-769)
1-29-86

Chemical: COMMAND (FMC 57020, Dimethazone)

Caswell No.: 463D

Petitioner: FMC Corporation

Petition No.: 4F3128

Background: The Branch had previously recommended that tolerance request for the use of COMMAND on soybeans be denied (Gregorio to Taylor, August 20, 1985). This recommendation was based on an insufficient toxicology data base:

1.) The rat teratology study (FMC Study No. A83-1142, June 29, 1984) was classified as Supplementary and additional information was requested in concert with a request for a lab/data audit. The Branch's concern has been adequately satisfied (memo, Gregorio to Taylor, January 17, 1986 and January 21, 1986). Therefore, the rat teratology studied has been reclassified as Minimum.

005659

2.) The 2-year feeding/oncogenicity study in mice (FMC Study No. A81-651, July 25, 1984) was classified as Supplementary based on the Branch's decision that a Maximum Tolerated Dose had not been achieved. Subsequently, the Branch has utilized an internal policy decision making scheme for addressing the adequacy of chronic studies in which the MTD has not been achieved. In the case of this study, it has been determined that this study supports the current request for the soybean use.

8 POINT SUMMARY

1.) Summary of Toxicology Data Base Considered In Setting Permanent Tolerance:

COMMAND TECHNICAL (FMC 57020) DATA SUMMARY

| Study | Results | Tox Cat |
|---|---|---|
| Acute Oral-rats | $LD_{50}$ = 2077 mg/kg (M)<br>$LD_{50}$ = 1369 mg/kg (F) | III<br>III |
| Acute Dermal-rabbit | $LD_{50}$ = greater than 2000 mg/kg | III |
| Acute Inhalation-rat | $LC_{50}$ = 6.25 mg/L (M)<br>$LC_{50}$ = 4.23 mg/L (F) | III<br>III |
| 3-Month Feeding-dog | NOEL not established; insufficient animals sacrificed (2/sex/dose) | |
| 3-Month Feeding-mice | NOEL not established; liver cytomegaly seen at lowest dose tested (20 ppm) | |
| 3-Month Feeding-rat | NOEL not established; report incomplete | |
| 1-Year Feeding-dog [doses: 0, 100, 500, 2500, 5000 ppm for 1-year] | NOEL = 500 ppm (12.5 mg/kg/day)<br>LEL = 2500 ppm (62.5 mg/kg/day)<br>[increased liver weights, absolute and relative to body weight in males and females; increase in cholesterol] | |
| 2-Year Feeding-rat [doses: 0, 20, 100 500, 1000, 2000 ppm for 2-years; 4000 and 8000 ppm for 3-months] | NOEL = 100 ppm ( 4.3 mg/kg/day)<br>LEL = 500 ppm (21.5 mg/kg/day)<br>[lower bdy wt in 1000 and 2000 ppm males, 2000 ppm females; cholesterol increased in 500, 1000 and 2000 ppm females; SGOT decreased in 1000 and 2000 ppm females; increased liver | |

741

005659

| | |
|---|---|
| | weights, absolute and relative to body and liver weights in 500, 1000, 2000 ppm females; increased incidence of liver cytomegaly in 500, 1000, 2000 ppm males. |
| 2-Year Feeding-mice [doses: 0, 20, 100, 500, 1000, 2000 ppm for 2-years; 4000 and 800 ppm for 3-months] | NOEL = 100 ppm (15 mg/kg/day)<br>LEL = 500 ppm (75 mg/kg/day)<br>[increase in white blood cells in 500, 1000, 2000 ppm males; increase in SGOT and SGPT in 1000 ppm males at 24 months; increase in absolute liver weights at 1000 and 2000 ppm males; increase in liver cytomegaly in 1000 and 2000 ppm males; increase in lymphoid hyperplasia in 1000 and 2000 ppm females. |
| Teratology-rabbit [doses: 0, 30, 240, 1000 (reduced to 700 mg/kg/day from gestation days 13 thru 18) mg/kg/day] | Negative for teratogenicity at Highest Dose Tested, 700 mg/kg/day<br><br>Maternal NOEL = 240 mg/kg/day<br>Maternal LEL = 700 mg/kg/day<br>[decreased body weight]<br><br>Fetotoxic NOEL = 240 mg/kg/day<br>Fetotoxic LEL = 700 mg/kg/day<br>[increased number of resorptions] |
| Teratology-rat [doses: 0, 100, 300, 600 mg/kg/day) | Maternal NOEL = 100 mg/kg/day<br>Maternal LEL = 300 mg/kg/day<br>[decreased locomotion, genital staining, runny eyes]<br><br>Fetotoxic NOEL = 100 mg/kg/day<br>Fetotoxic LEL = 300 mg/kg/day<br>[increased incidence of delayed ossification]<br><br>Negative for teratogenesis |
| Mutagenicity-Reverse Mutation (Salmonella) [2 studies] | Negative with/without activation |
| Mutagenicity-Point Mutation (CHO/HGPT) | Weakly positive without activation<br>[Positive control:Benzopyrene; |

5
742

Command 3x background; "weakly positive"]

| | |
|---|---|
| Mutagenicity-In Vivo - Cytogenetics (chromosomal aberations) | Negative |
| Mutagenicity- Unscheduled Dna Synthesis | Negative |

2.) Summary of Toxicology Data Considered Desirable But Currently Lacking:

NONE

3.) Action Being Taken To Obtain Lacking Data:

NONE

4.) Summary of Temporary Tolerances Granted:

soybeans ---- 0.5 ppm residue

5.) Summary of How Total Tolerances Would Affect The MPI:

The %ADI that would be used by granting the soybean tolerance is 0.03. The TMRC is 0.0007 mg/kg/1.5 kg and the MPI is 2.5800 mg/day (60 kg).

6.) Acceptable Daily Intake Data:

The ADI (0.0430 mg/kg/day) is based on the 2 year feeding/ oncogenicity rat study (NOEL = 4.3 mg/kg/day; safety factor = 100).

7.) Pending Regulatory Action Against Registration:

NONE

8.) Other Considerations:

NONE

No CFR Number ** COMMAND 373/85

005659

Unverified Printout

ACCEPTABLE DAILY INTAKE DA **DRAFT**

NOEL change not recorded ssr

| RAT, Silver | NOEL | | S.F. | ADI | PDI |
|---|---|---|---|---|---|
| mg/kg | ppm | | | mg/kg/day | mg/day(60kg) |
| 4.300 | 60.00 | | 100 | 0.0430 | 2.5800 |

Unpublished, Tox Approved 132937

| Crop | Tolerance | Food Factor | mg/day(1.5kg) |
|---|---|---|---|
| Soybeans (oil)(249) | 0.050 | 0.92 | 0.00069 |

| PDI | TMRC | % ADI |
|---|---|---|
| 2.5800 mg/day(60kg) | 0.0007 mg/day(1.5kg) | 1.93 |

**********

BEST AVAILABLE COPY

744