1-29-86

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

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
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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.

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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) LD_{50} = 1369 mg/kg (F)	III III
Acute Dermal-rabbit	LD_{50} = greater than 2000 mg/kg	III
Acute Inhalation-rat	LC_{50} = 6.25 mg/L (M) LC_{50} = 4.23 mg/L (F)	III 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) LEL = 2500 ppm (62.5 mg/kg/day) [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) LEL = 500 ppm (21.5 mg/kg/day) [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	

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	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) LEL = 500 ppm (75 mg/kg/day) [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 Maternal NOEL = 240 mg/kg/day Maternal LEL = 700 mg/kg/day [decreased body weight] Fetotoxic NOEL = 240 mg/kg/day Fetotoxic LEL = 700 mg/kg/day [increased number of resorptions]
Teratology-rat [doses: 0, 100, 300, 600 mg/kg/day)	Maternal NOEL = 100 mg/kg/day Maternal LEL = 300 mg/kg/day [decreased locomotion, genital staining, runny eyes] Fetotoxic NOEL = 100 mg/kg/day Fetotoxic LEL = 300 mg/kg/day [increased incidence of delayed ossification] Negative for teratogenesis
Mutagenicity-Reverse Mutation (Salmonella) [2 studies]	Negative with/without activation
Mutagenicity-Point Mutation (CHO/HGPT)	Weakly positive without activation [Positive control:Benzopyrene;

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	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

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