RB-10346

4-31-85

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

D0462E

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Use of DPX-6025 on Soybeans

FROM: Thomas Edwards, Pharmacologist
Hazard Evaluation Division (TS-769)

TO: Robert Taylor, PM 25 / Viki Walters
Registration Division (TS-767)

THRU: Clint Skinner, Section Chief
Review Section III

and

Theodore Farber, Chief
Toxicology Branch, HED (TS-769)

Chemical: CLASSIC (DPX-F6025, INF-6025)

Caswell No.: 193B

EPA Registration No.: 352-UGA, 5F3186,

Accession Nos.: 073111, 073120, 258061.

Requested Actions: Comments concerning registration request and tolerance petition for use on soybeans

Comments:

Five studies (reviews are attached) were reviewed with the following results:

(1) 90-Day feeding mouse study. NOEL: 250 ppm, LEL: 125 ppm (centrilobular hepatocellular hypertrophy).

(2) Interim, first 12 months, report on 2-year feeding and 2-generation, 4-litter, reproduction rat study. NOEL: 250 ppm, LEL: 2500 ppm (decreased body weight of pups and dams).

(3) Interim metabolism study. Half of the radioactivity was eliminated in less than 59 hours. Most was eliminated 168 hours.

(4) 18-Months feeding, mouse. NOEL: 125 ppm, LEL: 1250 ppm

180
64

(5) Teratology,rabbit.
Not teratogenic.
Maternal toxicity
NOEL: 60 ppm. LEL: 300 ppm (decreased weight gain)
Fetal toxicity
NOEL: 15 ppm. LEL: 60 ppm (delayed ossification)

Two of the three mutagenicity studies which previously were considered to be not adequate have (because of comments and additional information) been upgraded to the Core Classification status, Acceptable. The studies are: (1) in vivo bone marrow study (No. 201-615), no clastogenic, chromasomal, or chromatid effect was seen. (HDT:5000 mg/kg). (2) Ames test. Cytogenicity data provided which indicated that no mutagenicity was found at the cytotoxic dose level.

The Unscheduled DNA Synthesis study, No.208-83, although apparently conducted according to adequate procedures, has an omission. The choice of highest dose was not justified. No toxic dose was tested. Unless 10 m M represents the limit concentration for such studies, ie. 5000 micrograms, cytogenic data is needed. Pending the receipt of such data or appropriate information, the study is inconclusive. However, when toxicity data (or limit dose) or solubilityy criterion information has been provided, the study may be upgraded to Acceptable.

Inerts have been cleared.

Additional data is needed before registration.

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TOXICOLOGY BRANCH DATA REVIEW

Study Type: Four-weeks range finding and 90-days feeding, mouse.

Accession Number: 073111(5)

MRID Number:

Sponsor: DuPont, HLR 337-83

Contracting Lab:

Date: 11-7-83

Test Material: DPX-F6025(INF-6025)

EPA Evaluation Review. Thomas Edwards (Thomas Edwards) 7-31-85 (Date)

Review Section Approval. Clint Skinner (Clint Skinner) 8-20-85 (Date)

Protocol: See procedures attached.

Results:

A. After 4 weeks

Ten mice from each group were killed and necropsied at that time.

No adverse clinical signs were reported.

In males, an increase in mean absolute liver weight was found in the 2,500, 5,000 and 7,500 ppm groups and increased relative liver weights in the 125, 625, 1,250, 2,500, 5,000, and 7,500 ppm groups. Increased mean absolute and relative spleen weights were found in the 2,500 ppm group.

In females of the 25 ppm group, decreased mean absolute and relative liver weights were found. Increased mean absolute and relative liver weights were found in the 5,000 and 7,500 ppm groups. Decreased mean absolute kidney weights were found in the 2,500 and 5,000 ppm groups.

Based on these results, only the 0, 25, 125, 1,250 and 5,000 ppm groups were continued in the 90-day study.

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B. The 90-Day study

Two deaths occurred during the study. One female of the 1,250 ppm group and one male of the 5,000 ppm group. There were no treatment related clinical signs reported. No treatment related hematological changes were reported.

There was no report of clinical chemistry results.

Statistically significant increased mean absolute and relative liver weights were found in males and females at 5 000 ppm levels (Tables XVI - XIX). Also increased values at the 1,250 ppm level indicated a dose-response trend.

Mean relative kidney weights were statistically high in the 125 ppm groups. This was not dosage-response related.

No macroscopic pathology was reported for the 90-day study. Treatment related centrilobular hepatocellular hypertrophy was found at all levels above 125ppm. One male out of ten at the 25 ppm had this hypertrophy. This was considered to be a borderline effect for this reversible lesion(Table III).

Conclusions:

NOEL: 125 ppm
LEL: 1250 ppm (centrilobular hepatocellular hypertrophy).

Core Classification:

Minimum

Toxicology review of Classic

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TOXICOLOGY BRANCH DATA REVIEW

Study Type: Interim report on 2-year feeding and 2-generation, four litter reproduction study, rat.

Accession Number: 073111(6)

MRID Number:

Sponsor: DuPont, HLR No. 357-84

Contracting Lab:

Date: 10-25-84

Test Material: DPX-F6025(INF-6025)

EPA Evaluation Review. Thomas Edwards (Thomas Edwards) 7-31-85 (Date)

Review Section Approval. Clint Skinner (Clint Skinner) 8-14-85 (Date)

Introduction:

The interim report includes 1 year of feeding and one generation of the reproduction study.

Protocol: See procedure attached.

Results:

A. Feeding Study, First 12 Months

No treatment related deaths were reported. Some variability of mean body weight gain was observed. Mean body weights in males of the 2,500 ppm group were significantly less than controls only during the early part of the study (Table 2). The only group which was statistically less than controls at the end of the year was the female 2,500 ppm group. This group was statistically less throughout the first year (Table 3 and Figures 1 and 2).

The food consumption and food use efficiency of the female 2,500 ppm group were somewhat lower than for controls but not significant statistically and this did not appear to account for lower weight gains.

There were small and possibly dosage-related decreases in absolute and relative spleen weights which were statistically significant at the 2,500 ppm level in males (Tables 15-16).

Several hematological and chemical chemistry effects observed in males and females at the 2,500 ppm dosage level were apparently treatment related. These included decreased hematocrit and increased serum globulin

No treatment related gross or histopathology was reported.

B. Reproduction Study. First 12 Months

No effects on reproduction or lactation was reported.

Body weights of male and female pups were lower in F_{1A} and F_{1B} generations of the 2,500 ppm groups. The male and female pups of F_{1A} and female pups of F_{1B} were signigicantly lower statistically. Also dam body weights were lowered (Tables 20 and 22).

Conclusions:

A. Feeding Study. First 12 Months

Several significant effects were observed in the 2,500 ppm groups. These included the following: body weights were significantly lower in females than for controls; Decreases in absolute and relative spleen weights; Decreased hematocrit and increased serum globulin.

NOEL: 250 ppm
LEL: 2,500 ppm (body weights, organ weights clinical chemistry and hematology)

B. Reproduction Study. First 12 Months

Body weights of pups and dams of the 2,500 ppm groups were statistically lower than controls.

NOEL: 250 ppm
LEL: 2,500 ppm (body weights, pups and dams)

Core Classification:

Minimum for first 12 months of feeding study.

Minimum for first 12 months of reproduction study.

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TOXICOLOGY BRANCH DATA REVIEW

Study Type: Interim report on metabolism, rat

Accession Number: 07312007

MRID Number:

Sponsor: DuPont, No. AMR-220-84

Contracting Lab:

Date: 1984

Test Material: ^{14}C-DPX-F6025

EPA Evaluation Review. Thomas Edwards — Date 7-31-85

Review Section Approval. Clint Skinner — Date 8-19-85

Protocol: See attached procedures.

Results:

No exhaled readioactivity was detected. Excretion in feces and urine was about equal after both low or high dose.

One-half the radioactivity was excreted (total in urine and feces) by males in 48 hours or less and by females in 58 hours or less. Most but not all was eliminated in 168 hours (figures 6, 7,8,9,10, and 11).

The general distribution of radioactive residue for those killed at 168 hours is shown in tables VIII, IX, and X.

Figure 16 and 18 indicate that little if any unmetabolized DPX-F6025 was found in urine. It is unclear whether or not urine from the high dose group was included to obtain these data. DPX-F6025 and metabolites were found in the feces.

Attempts to elucidate metabolic pathways after identifying some of the metabolites are reflected in the proposed schemes shown in figures 21A and 21B.

Conclusions:

No exhaled radioactivity was detected. Elimination in urine and feces was about equal.

Half of radiolabel was eliminated in less than 59 hours and most was eliminated in 168 hours.

Core Classification:

Acceptable interim report.

Toxicology review of Classic

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Toxicology Branch
Data Review

Study Type: Teratology, rabbit

Accession Number: 258061 (10)

MRID Number:

Sponsor: DuPont, HLR 14-85

Contracting Lab:

Date: January 23, 1985

Test Material: DPX-F6025 (INF-6025)

EPA Evaluation Review. Thomas Edwards (Thomas Edwards) 7-31-85 (Date)

Review Section Approval. Clint Skinner (Clint Skinner) 9-19-85 (Date)

Protocol: See attached Materials and Methods.

Results:

Two does died. One control and one from high dosage group.

No adverse clinical signs were reported.

Significantly reduced food consumption and reduced body weight gains were observed in dams of the 300 ppm group.

Statistically significant increases in percent of fetuses with delayed ossification in the 60 and 300 ppm groups were found. No increases in incidence of teratogenic malformations were reported (tables 7 and 8).

Conclusion:

DPX-F6025 was not shown to be teratogenic.

Maternal toxicity NOEL 60 ppm
LEL 300 ppm (decreased weight gain).

Fetal toxicity NOEL 15 ppm
LEL 60 ppm (delayed ossification).

Core Classification:

Minimum

Toxicology review of Classic

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Toxicology Branch
Data Review

004626

Study Type: 18-Month feeding, mouse

Accession Number: 2X5061(9)

MRID Number:

Sponsor: DuPont, HLR No. 94-85

Contracting Lab:

Date: March 27, 1985

Test Material: DPX-F6025 (INF-6025)

EPA Evaluation Review. Thomas Edwards (Thomas Edwards) 7-31-85 (Date)

Review Section Approval. Clint Skinner (Clint Skinner) 9-19-85 (Date)

Protocol: See attached Materials and Methods.

Results:

Lower mean body weights were found in all treated groups compared to controls. Some differences were statistically significant. Food consumption values were also lower in treatment groups, but food efficiency values were similar to respective controls. Physiological effects of DPX-F6025 on body weights is not clear.

Unscheduled deaths per group ranged from 13 to 24 percent. There was no relationship to treatment.

Clinical observations, clinical chemistry, hematology, gross and microscopic pathology revealed no apparent treatment-related effects.

Conclusion:

No treatment-related effects were demonstrated after 18 months. However, the results of the 90-day mouse study must not be overlooked. Included in our considerations is the 90-day study No. HLR 337-83, which results in the following:

NOEL: 125 ppm
LEL: 1250 ppm (centrilobular hepatocellular hypertrophy at 90 days.)
Negative for oncogenicity (H D T , 1,250 ppm)

Core Classification:

Minimum

Toxicology review of Classic

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