CASWELL FILE

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

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Subject: Section 18 for wheat, barley for DPX-M6316 (Harmony)

To: Jack Housenger, PM-41
Registration Division, TS-767C

From: Marcia van Gemert, Ph.D.
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Thru: Theodore M. Farber, Ph.D.
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Chemical: DPX-M6316 (Harmony)

Caswell No: 573S

Project No: 7-0307

EPA ID NO. 87-VA-01/87-VA-02

Action Requested: Can this use be toxicologically supported on wheat and barley? Please include one-liners.

The state of Virginia has requested a tolerance for Harmony on wheat and barley.

Previous submissions had supported a temporary tolerance for wheat and barley. The April 11, 1985 Toxicology Branch memo lists the studies on DPX M6316 technical which have been submitted. These include:

DPX-M6316 technical:

1. Acute Oral LD_{50}: 5000 mg/kg, IV. Core guideline

2. 4-hour inhalation LC_{50}, rat: 7.9 ml/L, Tox category III. Core minimum

3. Acute Dermal LD_{50}, Rabbit: 2000 mg/kg, tox category III, core minimum

4. 90-day feeding study in rats: NOEL = 100 pm , LEL = 2500 ppm MTD = 7500 ppm, core minimum

5. One generation reproduction rat: acceptable as range finder only,

6. 13-week feeding study- dog: NOEL = 1500 ppm. LEL = 7500 ppm (body and adrenal weight reduced in males) Core minimum

7. Teratology rat: Noel for fetotoxicity and teratogenesis:159 mg/kg
LEL for fetotox. and teratogenesis: 725 mg/kg
Core classification : minimum

DPX-M6316

1. acute oral LD_{50} in rat: 5000 mg/kg, tox category IV, core guideline

2. Acute dermal LD_{50} in rabbits: 2000 mg/kg, tox category III, core minimum

3. Dermal sensitization: not a sensitizer, core minimum

A PADI of 0.005 mg/kg/day was based on a NOEL of 10 mg/kg/day from a 90-day rat subchronic feeding study with a safety factor of 2000.

The proposed temporary tolerance at that time of 0.05 ppm on barley and wheat resulted in a TMRC of 0.0078 mg/day using 2.6% of the MPI of 0.3000 mg/kg/day.

More recently (7/7/86) Dupont has submitted more data on Harmony. Most of these data have been reviewed, however, some studies are still outstanding at the Dynamac contractor and won't be expected to be delivered until sometime in the middle of March, 1987. These studies that have been reviewed are briefly summarized below.

1. Acute oral toxicity in rats, Study report # 90-83, 3/23/83
Acute oral toxicity > 11,000 mg/kg body weight
core classification = minimum

2. Mouse oncogenicity study, report # HLR 685-85 date 6/26/85
At terminal sacrifice there was a significant drop in body weight at 750 and 7500 ppm dose levels. Based on these effects the NOEL = 25 ppm and LEL = 750 ppm. Core Classification = supplementary, no individual pathology sheets for each animal accompany this study report.

3. Chronic/oncogenicity study in rats. Study report # 4980-001 #261-86. 6/26/86 Core classification: supplementary
There are several deficiencies in this study which will need to be corrected or explanations given.
1. Individual pathology sheets will need to be submitted.
2. An explanation will need to be given as to why several clinical chemistry parameters such as chloride, phosphorous, total bilirubin and creatinine phosphokinase were not investigated, especially when there were electrolyte effects.
3. An explanation will need to be given as to why ophthalmological examinations were not performed.
4. The clinical chemistry tables should be submitted in a clearer form.
There is a decrease in serum sodium levels at all doses levels

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tested with no no-effect level evident.

4. 1-year dog study. Study report # 201752 June 21, 1986. Core classification: supplementary, pending receipt of stability data and actual test compound concentrations in the diet. Dupont has not made it clear why they did not have all the recommended clinical chemistry parameters such as chloride, phosphorous and SGPT investigated, especially when there appeared to be some liver involvement in this study, and electrolyte involvement in the rat study. Also, no opthalmological exams were performed. Based on increased liver weights in the high dose males and increased thyroid/parathyroid-to-body weight ratios in females at the high dose, and some indications of decrased body weight and body weight gain in females after 22 weeks, the NOEL should be 750 ppm with an LEL of 7500 ppm.

5. Metabolism in rats: study report # 234-86, May 14, 1986. Core classification, minimum
Most of the radioactivity was recovered in the urine and feces with almost no tissue and carcass accumulation of radioactivity. Of the radioactivity eliminated in the urine and feces, most was parent compound with 3 minor metabolites. Three minor metabolites also appeared in some fecal samples but remained unidentified.

6. Metabolism in rats: Study report # 91-86, 4/25/86 Core classification: along with the first metabolism study submitted concurrently, minimum.
As found in the first metabolic study, most of the radioactivity was recovered in the urine and feces with almost no tissue and carcass accumulation of radioactivity. Of the radioactivity eliminated in the urine and feces, most was parent compound with three minor metabolites. Five minor metabolites appeared in the urine and three appeared in the fecal samples which remained unidentified.

7. 4-week rangefinding and 90-day subchronic study in mice. Study report # 466-83, June 15, 1984. Core classification: supplementary. The study is missing clinical chemistry data, opthalmological examinations and raw data. NOEL > 7500 ppm. No effects were seen at any of the doses tested. However, it meets the MTD criteria in mice (7000 ppm top dose).

8. Mutagenicity- Reverse mutation in Salmonella typhimurium, Study report # 235-83, 1986. Core classification: acceptable. Under the conditions of two independent Salmonella typhimurium reverse mutation assays, INM-6316-7 at doses ranging from 0.1 to 20 ug/place, both in the presence and absence of S9 activation, did not induce a mutagenic response in S. typhimurium TA1535, TA97, TA98, or TA100. Cytotoxic was excessive at the next higher dose (50 ug/plate), showing that a high dose of 20 ug/plate was adequate.

Reviews of the teratology and reproduction studies have not been completed. As mentioned above these are supposed to be received back from the contractor by the middle of March.

It doesn't appear from the data presented that anything more than

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temporary tolerances or section 18's can to be supported until some of the questions raised by the submitted studies can be answered.