CASWELL FILE

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

MAR 17 1987

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Subject Review of data for new chemical, "Harmony"

To Taylor V. Walters
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 2129

EPA ID NO. 6F 3431/ 352-UUA

Action Requested Review the tolerances and registration of the new chemical DPX- M6316

Comments The Registration division has requested a review of the submitted toxicology studies. Many of these studies contain numerous deficiencies which will need to be corrected before any permanent tolerances or registration can be granted. The previously submitted studies are listed below with more substantial comments for the most recently submitted data following.

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 developmental toxicity: 159 mg/kg
LEL : 725 mg/kg
Core classification : minimum

DPX-M6316 - HARMONY

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 more detailed review of the recently submitted studies on DPX-M6316 technical is 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 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, ophthalmological 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.

9. Teratology study in rabbits: Study # MR-7108-001 dated April 0, 1985 from Haskell Laboratories.
the NOEL and LOEL for maternal toxicity are approximately 158 and 511 mg/kg/day (these are the reported doses received by animals in the 200- and 650 mg/kg/day groups, respectively), based on mild reductions in maternal body weight gain at 511 mg/kg/day.
Although the fetotoxic potential of the test material could not be ruled out (based on slight, nonsignificant decreases in fetal body weights at 511 mg/kg/day and on mild, nonsignificant increases in fetal and litter incidences of subcutaneous hemorrhages in all groups exposed to the test material), the noted effects were of negligible biological importance.

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Therefore the NOEL for developmental toxicity was greater than 511 mg/kg/day, the highest dose tested.

Classification- core minimum

10. Two-generation reproduction study in rats, Study # 432-85, dated Dec. 3, 1985. Haskell Laboratories.
The LELs for parental, reproductive or developmental toxicity of INM-6316 in rats could not be established since no toxic effects were demonstrated at any of the dose levels tested, (i.e. 25, 500, and 250 ppm); therefore, the NOEL for this study was 2500 ppm, the highest dose level tested.
Recommendations:
If further work is conducted it is recommended that:
1. The reproductive/developmental toxicity of the test material be tested at higher dose levels, levels that would produce parental or other toxicity.
2. More animals/sex/group be assigned to the study to provide at least 20 pregnant females per group.
3. More complete postmortem procedures for parental animals be implemented.
4. Individual and summarized data be presented for food consumption, gestation lengths, precoital intervals, and the numbers of breeding pairs with evidence of copulation be given.

Core classification: supplementary