Copies to: [redacted]

REVISED REPORT

E. I. du Pont de Nemours and Company
Haskell Laboratory for Toxicology and Industrial Medicine

HASKELL LABORATORY REPORT NO. 721-78 [redacted]

| Material Tested* | Haskell No. | Other Codes | Sample Ready for Testing | Submitted by |
|---|---|---|---|---|
| [redacted] | 12,398 | [redacted] | 7-6-78 | [redacted] CD&P Department, Jackson Lab., Chambers Works |

TEN-DOSE ORAL SUBACUTE TEST [redacted]

Procedure: The test material, as an aqueous solution, was administered by intragastric intubation to a group of ten young adult ChR-CD male rats, five times a week for two weeks, at a repeated dosage level of 3,400 mg/kg/day; an additional group of ten rats served as controls and was intubated with distilled water. Five control and five test rats were sacrificed approximately two-four hours after the last dose. The remaining five control and five test rats were sacrificed 14 days after the last dose.

Results:

| Dose (mg/kg/day) | No. of Doses | Mortality | Clinical Signs |
|---|---|---|---|
| 3,400 | 10 | 0/10 | First Week: Sporadic weight loss. |
| | | | Second Week: Sporadic weight loss. |
| | | | Recovery Period: None. |

Pathologic Changes:** Gross and microscopic compound-related changes were observed in the livers of rats examined on the last day of dosing. The mean absolute liver weight of test rats was 40% greater than that of the control group. The liver weight of test rats examined after a 14-day recovery period was 26% greater than the control group. Histologically, liver hypertrophy was observed in test rats. These changes appeared to be reversible although not completely during the 14-day recovery period.



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Summary: [redacted] was administered orally to young adult ChR-CD male rats at a repeated dose level of 3,400 mg/kg/day for ten days over a two-week period. The compound-related pathological effect was hypertrophy of the liver. The changes observed would be expected to be completely reversible if given a longer recovery period.

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[redacted]

** Tissues examined histologically by [redacted] included: liver, kidneys, lungs, brain, adrenals, heart, spleen, sternal bone marrow, eyes, upper and lower gastrointestinal tracts, epididymides, testes, thyroid, parathyroid, pancreas, thymus, lymph nodes and trachea.

Report by: T. Q. Dilworth
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TQD/aph
[redacted]
Report No. 721-78
Date Issued: December 1, 1978
Date Revised: December 22, 1978

Copies to: [redacted]

E. I. du Pont de Nemours and Company
Haskell Laboratory for Toxicology and Industrial Medicine

HASKELL LABORATORY REPORT NO. 52-79 [redacted]

| Material Tested | Haskell No. | Other Codes | Sample Ready for Testing | Material Submitted by |
|---|---|---|---|---|
| [redacted] | 12,402 | [redacted] | 7/6/78 | [redacted] Chemicals, Dyes & Pigments Dept. Jackson Laboratory Chambers Works |

## TEN-DOSE ORAL SUBACUTE TEST [redacted]

Procedure: The test material, as a 50% suspension in acetone/corn oil 15:85 or 7.5:92.5, was administered by intragastric intubation to a group of 10 young adult ChR-CD male rats at a repeated dosage level of 3,400 mg/kg/day; an additional group of 10 rats served as controls and was intubated with acetone/corn oil 15:85 or 7.5:92.5. Eight test rats died before the fifth dose and the remaining two test rats were sacrificed the day after the fourth dose. Two control rats were sacrificed after the fourth dose. Four of the remaining eight controls were sacrificed after the tenth dose and the remaining four were sacrificed after a 14-day recovery period.**

The test material, as an 18% suspension in acetone/corn oil 15:85, was administered by intragastric intubation to a group of 10 young adult ChR-CD male rats at a repeated dosage level of 1,700 mg/kg/day; an additional group of 10 rats served as controls and was intubated with acetone/corn oil 15:85. Ten test rats died before the sixth dose. Two control rats were sacrificed after the seventh dose and the remaining eight controls were sacrificed without pathology.***

The test material, as a 7% suspension in acetone/corn oil 15:85, was administered by intragastric intubation to a group of 10 young adult ChR-CD male rats at a repeated dosage level of 850 mg/kg/day; an additional group of 10 rats served as controls and was intubated with acetone/corn oil 15:85. Four test rats died before the tenth dose and three of the remaining six test rats were sacrificed approximately four hours after the tenth dose, and three after a 14-day recovery period. Five control rats were sacrificed after the tenth dose and the remaining five controls were sacrificed after a 14-day recovery period.


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Result

| Dose (mg/kg/day) | No. of Doses | Mortality | Clinical Signs |
|---|---|---|---|
| 3,400 | 2-4 | 8/10 | First Week: Stained and wet perineal area, stained face, diarrhea, lacrimation, prostration, and weight loss. |
| 1,700 | 3-5 | 10/10 | First Week: Diarrhea, humped posture, congestion stained face, stained and wet perineal area, weakness, and weight loss. |
| 850 | 3-10 | 4/10 | First Week: Stained and wet perineal area, stained face, diarrhea, lacrimation, weakness, humped posture, and weight loss.<br>Second Week: Piloerection, unkempt fur, humped posture, weakness, stained and wet perineal area, stained face, eyes half-closed, and weight loss. |

Recovery Period: None

Pathologic Changes:**** See Appendix (Pathology Report No. 2-79).†

Summary: [redacted] was administered orally to groups of young adult ChR-CD male rats at repeated dose levels of either 3,400 mg/kg/day (2 to 4 days), 1,700 mg/kg/day (2 to 5 days), or 850 mg/kg/day (3 to 10 days). Severe weight loss and mortalities were observed in all 3 groups. Histopathologic changes involving the lungs, gastrointestinal tract, liver, spleen, thymus, sternal bone marrow, epididymis, testes, renal tubules, heart, and hematopoietic cells were observed in the treated rats. Following a 14-day recovery period, histopathologic changes among rats in the 850 mg/kg group were confined to the liver (with 1 rat also showing atrophic testes).

[redacted]

** These animals served as a common control group for H-12,402 and H-12,403.

*** These animals served as a common control group for H-12,402 and H-12,396.

**** Tissues examined histologically by [redacted] included: lungs, gastrointestinal tract, exterior body surface, liver, heart, spleen, thymus, sternal bone marrow, epididymis, testes, renal tubules, hematopoietic system, kidneys, brain adrenals, thyroid, parathyroid, eyes, trachea, stomach, duodenum, pancreas, cecum, colon, esophagus, and lymph nodes.

† There will be a supplemental pathology report for the 3,400 mg/kg/day dose level animals when histology is complete.



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LH:vlm
Date Issued: March 16, 1979
[redacted]
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