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

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SEP - 2 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: UDMH - Submission of a 1-Year Interim Report of the 2-Year Chronic Oncogenicity Study in Rats

TOX Chem No.: 366G
Project No.: 8-0857

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and

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Under a cover letter dated May 2, 1988, Raymond A. Cardona of the Uniroyal Chemical Company, Inc., has submitted a 12-month interim report on a study entitled "Two-Year Oncogenicity Study in Rats." The interim report has been evaluated and the following findings were noted:

- There was a dose-related increase in the incidence of corneal opacity in all female treated groups during the intervals 27 to 39 weeks and 40 to 52 weeks.

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- Water consumption was decreased in males and females in the mid- and high-dose groups.

- Females in the high-dose group had an increase in the incidence of pituitary hyperplasia and basophilic cytoplasmic alteration in the salivary gland.

It was noted that there were several instances in which the incidence of "corneal opacity" observed at 52 weeks, as reported in Appendix F - Individual Clinical Findings did not match the incidence of "cornea, cloudy" as reported in Table 9 - Incidence of Macroscopic Observations at 12 months. This apparent discrepancy should be addressed.

The report is classified as Core-Supplementary.

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Reviewed By: William B. Greear, M.P.H.
Section VII, Toxicology Branch (TS-769C)
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Section VII, Toxicology Branch (TS-769C)

DATA EVALUATION REPORT

Study Type: 2-Year Oncogenicity Study in Rats (1-Year Interim Report)

TOX Chem No.: 366G
MRID No.: 406135-02 (3 Volumes)

Accession No.: N/A

Test Material: UDMH

Synonyms: Dimethylhydrazine; N,N-Dimethylhydrazine; 1,1-Dimethylhydrazine

Study No.: IRDC Study No. 399-062

Sponsor: Uniroyal Chemical Company, Inc.

Testing Facility: International Research and Development Corporation
Mattawan, MI 49071

Title of Report: Two-Year Oncogenicity Study in Rats

Author: Dale E. Johnson

Report Issued: April 28, 1988

Conclusions:

See Discussion section for preliminary results. No NOEL or LEL has been established at this time. The NOEL and LEL will be established after evaluation of the final report.

Classification: Core-Supplementary

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A. Materials:

1. Test Compound - UDMH; Description: clear liquid; Batch No. Ref. JS-87, AC 931/018; JS 70, E732/140; JS-100, AC 931/036; JS-111, AC 897/072; JS 117, AC 897/100; JS 126, AC 931/125; JS-137, AC 931/146; JS 149, AC 957/017; JS 149, AC 957/017; JS 153, AC 957/034; JS 155, AC 957/034; JS 165, AC 957/064; JS-166, AC 957/066; JS 168/AC 975/077; JS 171, AC 957/084, and JS 182, AC 957/111; Purity: 100 mg UDMH Free Base/mL 1 N HCl; Contaminants: not reported.

2. Test Animals - Species: rat; Strain: Charles River Fischer 344; Age: 39 days old at start; Weight: males (80 to 110 g), females (70 to 90 g); Source: Charles River Breeding Laboratories, Inc., Kingston, NY.

B. Study Design:

1. Animal Assignment - Animals were assigned randomly to the following test groups:

Test Group	Dose in Drinking Water (ppm)	Main Study 24 Months Male	Main Study 24 Months Female	Interim Sac. 12 Months Male	Interim Sac. 12 Months Female
1. Control	0	50	50	20	20
2. Low (LDT)	1	50	50	20	20
3. Mid (MDT)	50	50	50	20	20
4. High (HDT)	100	50	50	20	20

2. Dosing Solution Preparation - Dosing solutions were prepared 3 times weekly. The control solution (deionized water with 25% citrate buffer) was also prepared 3 times weekly. The low dose was prepared by first making up a 1 percent base solution. The appropriate volume of the 1 percent base solution was then incorporated with the appropriate amount of vehicle to yield the low dose. The mid and high doses were prepared by incorporation of the test material with the appropriate amount of vehicle. The dosing solutions were stored at room temperature. A sample of each batch of test material was analyzed for purity. The stability of the dosing solutions stored under laboratory conditions was determined during the first month of study and at 6-month intervals. The concentration of the dosing solutions was determined at the first preparation of week 1 and twice monthly thereafter. The pH of the test solutions was measured after each sample was prepared.

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Results - The concentration of UDMH in the test material maintained at room temperature was determined to contain 93 to 115 percent of the claimed concentrations (usually 100 mg/mL). The stability of the test material in the dosing solutions analyzed 3 days after preparation on three separate occasions (weeks 1, 32, and 52) was found to contain 99 to 119 percent of the initial concentrations. Periodic analysis of dosing solutions at 2- to 3-week intervals yielded concentrations ranging from 91 to 120 percent of the target levels.

3. Animal Maintenance - Prior to study initiation the animals were observed for an 11-day acclimation period. The serum of the rats was analyzed for the presence of: Pneumonia virus of mice, Reovirus type 3, Encephalomyelitis (GDV II), Kilham rat virus, Toolan H-1, Sendai, Mouse adenovirus, lymplocytic, choriomeningitis, Rat coronavirus and SDA. The rats were individually housed in suspended wire-mesh cages in a controlled environment at a temperature of 75 ± 4 °F, humidity of 50 ± 8.5 percent and a 12-hour on/12-hour off light cycle. The room received 6 to 10 air changes per hour. Certified Rodent Chow #5002 and water were available ad libitum.

4. Statistics - Body weights, food consumption, water consumption, and hematological parameters were analyzed by one-way analysis of variance and Bartlett's test for homogeneity of variance. Test groups were compared to controls (by sex) using the appropriate t-statistic (for equal or unequal variance). Dunnett's multiple comparison tables were used to determine the significance of the differences. All tests were two-tailed with $p < 0.05$ and $p < 0.01$ used as levels of significance.

5. Quality assurance inspections were conducted 32 times during the 52-week period. The statement was signed by M.J. Wirth on April 28, 1988.

C. Methods and Results:

1. Observations - Observations of animals for moribundity, mortality, and overt signs of toxicity were performed twice a day. Detailed observation of animals for appearance and condition, behavior and activity, excretory function, respiration, orifices, eyes and palpable masses were conducted at least once a week.

Results - The number of deaths occurring within 52 weeks is listed on the following page.

Number of Deaths/Number of Animals

Dose Group							
Control		Low		Mid		High	
Male	Female	Male	Female	Male	Female	Male	Female
0/70	2/70	1/70	0/70	0/70	0/70	0/70	0/70

There were no significant differences among the control and test groups with respect to mortality. The incidence of corneal opacity was increased in all female treated groups during the periods weeks 27 to 39 and 40 to 52. The increases displayed dose-response relationships.

Incidence of Corneal Opacity in Females

Interval: Week 27 to 39

Lesion	Dose Group: Control	Low	Mid	High
Corneal Opacity (No. Affected/ No. Treated)	1/70 (1.4%)	2/70 (2.9%)	6/70 (8.6%)	6/70 (8.6%)

Interval: Week 40 to 52

Corneal Opacity (No. Affected/ No. Treated)	1/70 (1.4%)	5/70 (7.1%)	8/70 (11.4%)	10/70 (14.3%)

A similar finding of an increased incidence of corneal opacity was not evident in the male test groups.

2. Body Weights - Individual animal body weights were determined prior to study initiation, at weekly intervals for the first 16 weeks, and once every 4 weeks thereafter.

   Results - There were statistically significant reductions in weekly body weights (for several weeks) in females in the mid-dose group and males and females in the high-dose group when compared to controls.

3. Food and Water Consumption and Compound Intake - On a g/kg bwt/day basis, food consumption was comparable among the control and treated groups. On a g/kg bwt/day basis, water consumption was decreased in males and females in the mid- and high-dose groups. Compound intake was not addressed, however a table was presented. During the

first 52 weeks, compound intake ranged from 0.047 to 0.129, 4.65 to 12.269, and 6.808 to 17.637 mg/kg/day for males in the low-, mid-, and high-dose groups, respectively. Compound intake ranged from 0.074 to 0.148, 6.941 to 14.176, and 9.490 to 19.879 mg/kg/day for females in the low-, mid-, and high-dose groups, respectively.

4. Blood was collected from 10 rats/sex/group at 6 and 12 months for hematology and clinical analysis. The CHECKED (X) parameters were examined.

a. Hematology

X	Hematocrit (HCT)*		Total plasma protein (TP)
X	Hemoglobin (HGB)*	X	Leukocyte differential count
X	Leukocyte count (WBC)*	X	Mean corpuscular HGB (MCH)
X	Erythrocyte count (RBC)*	X	Mean corpuscular HGB conc. (MCHC)
X	Platelet count*	X	Mean corpuscular volume (MCV)

Results - The parameters were similar among control and treated groups at 6 and 12 months.

b. Clinical Chemistry - Not determined.

5. Urinalysis - Not determined.

6. Sacrifice and Pathology - All animals that died or were sacrificed on schedule (20/sex/dose) were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination.

X	Digestive System	X	Cardiovasc./Hemat.	X	Neurologic
	Tongue	X	Aorta*	X	Brain*
X	Salivary glands*	X	Heart*	X	Periph. nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Duodenum*	X	Spleen*	X	Eyes (optic n.)*
X	Jejunum*	X	Thymus*		Glandular
X	Ileum*		Urogenital	X	Adrenals*
X	Cecum*	X	Kidneys*		Lacrimal gland
X	Colon*	X	Urinary bladder*	X	Mammary gland*
X	Rectum*	X	Testes*	X	Parathyroids*
X	Liver*	X	Epididymides	X	Thyroids*
	Gallbladder*	X	Prostate		Other
X	Pancreas*	X	Seminal vesicle	X	Bone*
	Respiratory	X	Ovaries	X	Skeletal muscle*
X	Trachea*	X	Uterus*	X	Skin
X	Lung*			X	All gross lesions and masses

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Results

a. Organ Weight - Not determined.

b. Gross Pathology - There were no significant differences among the control and treated groups. There were several occasions in which the incidence of "corneal opacity," observed at week 52, reported in Appendix F - Individual Clinical Findings was not the same as reported for "corneal, cloudy" reported in Table 9 - Incidence of Macroscopic Observations at the 12-month interim sacrifice. This requires clarification.

c. Microscopic Pathology

1. Non-neoplastic - There was a slight increase in the incidence of pituitary hyperplasia in females in the high-dose group when compared to controls. The incidence for controls and for the LDT, MDT, and HDT was 3/22, 5/20, 5/20, and 7/20, respectively. There was also a slight increase in basophilic cytoplasmic alteration in the mandibular salivary gland in females in the high-dose group. The severity was indicated as "trace" and the incidence for controls and for the LDT, MDT, and HDT was 0/22, 1/20, 1/20, and 4/20, respectively. (It is noted that the investigator failed to statistically analyze the data.)

2. Neoplastic - Unremarkable.

D. Discussion:

There was no significant difference in the mortality rate among control and treated groups at 12 months. There was a dose-related increase in the incidence of corneal opacity in all females treated groups during the intervals 27 to 39 weeks and 40 to 52 weeks. There were significant reductions in weekly body weights over periods of several weeks for females in the mid-dose group and both males and females in the high-dose group. Food consumption was comparable among control and treated groups. Water consumption was decreased in males and females in the mid- and high-dose groups. The results of the hematology examinations were comparable among the control and treated groups. The results of the gross pathology examination were unremarkable. However, it was noted that there were several instances in which the incidence of "corneal opacity" observed at 52 weeks reported in Appendix F - Individual Clinical Finding was not comparable to the reporting of the incidence of "cornea, cloudy" in Table 9 - Incidence of Macroscopic Observations at

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12 months. This apparent discrepancy requires clarification. In the female high-dose group there were slight increases in pituitary hyperplasia and in basophilic cytoplasm alteration in the salivary gland. It was noted that the pathology data were not statistically evaluated. It would have been useful if they had been statistically evaluated.

A NOEL and LEL will be established after evaluation of the final report.

16277:I:Greear:LPC:CBI-03:KENCO:7/20/88:11/25/88:SG:EK
R:16385:Greear:LPC-CBI-03:KENCO:8/24/88:1/5/89:SG:psr:rw

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