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

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MAY 31 1988

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Subject: Review of a third 21-day dermal study on Whip

To: Richard Mountfort PM-23
Registration Division TS-767C

From: Marcia van Gemert, Ph.D. *10 van Gemert 5/27/88*
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Thru: Theodore M. Farber, Ph.D. *W.M.F. 5/27/88*
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Caswell No: 431C

Project No: 8-0587

Hoechst Celanese has submitted a third 21-day dermal study to satisfy the requirements of registration of Whip. The first and second 21-day dermal studies showed no NOEL for liver weights. In this study, doses of 0, 5, and 20 mg/kg were administered dermally for 21 daily doses to 10 animals/sex/group. No treatment-related mortality was seen. Group 3 females showed slight scaling of skin and slight maculate erythema during weeks 1 and 2. Group 3 females also showed slightly reduced food consumption during week 1 of treatment. No changes in liver weights were seen in treated animals. In this study an apparent decrease in absolute heart weights in the mid dose males and relative heart weights in mid and high dose males were not treatment-related, since they were not reproduced in the two previous 21-day dermal studies. This study now satisfies the 21-day dermal study requirement.
NOEL = > 20 mg/kg (HDT)

Classification = core minimum

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Reviewed by: Marcia van Gemert, Ph.D. *M. van Gemert 5/27/88*
Head, Section III, Tox. Branch (TS-769C)
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DATA EVALUATION REPORT

STUDY TYPE: 21-day dermal study

TOX. CHEM. NO.: 431C

ACCESSION NUMBER:

MRID NO.: 40523101

TEST MATERIAL: Fenoxypop ethyl

SYNONYMS: whip

STUDY NUMBER(S): A37374 Rcc 095455

SPONSOR: Hoechst Celanese Corp

TESTING FACILITY: RCC, Research and Consulting Co.

TITLE OF REPORT: Subacute 21-day repeated dose dermal toxicity with
HDE-033171 substance technical grade

AUTHOR(S): Ullmann, L., et al.

REPORT ISSUED: Dec. 21, 1987

CONCLUSIONS: Doses of 0, 5.0, and 20 mg/kg were given in 21 daily dermal applications to 10 animals/sex/group. No treatment-related mortality was seen. Group 3 females showed slight scaling of skin and slight maculate erythema during weeks 1 and 2. Group 3 females also showed slightly reduced food consumption during week 1 of treatment. No changes in liver weights were seen in treated animals, in contrast to the previous 21-day dermal study, where there was an apparent decrease in liver weights at all doses tested. In this study there was a decrease in absolute heart weights in males at 5 mg/kg and relative weights at 5 and 20 mg/kg which do not appear to be treatment-related, since they were not seen in the first study and therefore the phenomenon does not appear to be reproducible.
NOEL = > 20 mg/kg (HDT)

Classification: core-minimum

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A. MATERIALS:

1. Test compound: HOE-033171, Description solid, technical grade
Batch 80HZD980001, Purity 96.5%, contaminants: list in CBI appendix

Stability: stable

Stability of test article diluted: stable for at least 2 hours.

2. Test animals: Species: rat, Strain: Wistar, Age: males: 12 weeks
Weight: males: 204-228 gms, females 204-231 gms females: 14 weeks
Source: Kleintierfarm, Madoerin AG Switzerland

B. STUDY DESIGN:

1. Animal assignment

Animals were assigned 10/sex/group to the following test groups:

<u>Test Group</u>	<u>Dose in mg/kg</u>
1 Cont.	0
2 Low (LDT)	5
3 High (HDT)	20

Test article was prepared fresh daily.

METHOD: 21 dermal applications were administered to shaved skin of the back equivalent to around 10% of body surface. Test article was evenly applied and wrapped with an occlusive bandage for 6 hours/day. 5 days/week for a total of 21 dermal application days. Volume of applied test material or vehicle was 1.25 ml/kg body weight. After 6 hours of application the test article remainders were washed off with lukewarm tap water after termination of the daily treatment in all animals.

3. Animals received food (pelleted standard Kliba MO343 Batch 79/87 rat maintenance diet) and water ad libitum.

4. Statistics - The following procedures utilized in analyzing the numerical data are on appended pages 1 and 2.

5. Quality assurance was signed and certified.

C. METHODS AND RESULTS:

1. Observations

Animals were inspected daily for signs of toxicity and mortality.

Toxicity:local: Irritation was recorded prior to first treatment and daily thereafter. Erythema and edema was assessed according to a modified version of the Draize test with a scoring system below:

Erythema and eschar formation:

no erythema	0
slight erythema (barely perceptible)	1
well defined erythema	2
moderate to severe erythema	3
severe erythema (beet redness to slight eschar formation, injuries in depth)	4

Edema Formation:

No edema	0
slight edema (barely perceptible)	1
well defined edema (areas well defined by definite raising	2
moderate edema (raised approx. 1 mm)	3
severe edema (raised more than 1 mm and extending beyond the area of exposure)	4

Results: Mortality: none was seen

Clinical Signs: Local:

No treatment-related local effects were seen on the skin of males and females of groups 1 and 2 as well as group 3 males. Group 3 females showed slight scales (3) and slight maculate erythema (1) during weeks 1 and 2 at different times.

Systemic: No effects seen.

2. Body weight

Animals were weighed weekly during acclimation and the study.

Results: No effects were seen on body weights.

3. Food consumption and compound intake

Consumption was determined once during acclimation and weekly thereafter.

Results: Group 3 females showed slightly reduced food consumption during week 1 of treatment. No other effects were observed. Data are on appended page 3.

4. Ophthalmological examinations

Performed on all animals at termination of the experiment. According to the study text, "ten minutes after application of the mydriatic solution the cornea, lens and anterior chamber, vitreous body and ocular fundus of both eyes were examined under dimmed light using a Heine Microflex 2 ophthalmoscope."

Results: No treatment-related effects on the eyes were seen.

7. Sacrifice and Pathology -

All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs in addition were weighed.

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

- * Pharynx* required for subchronic and chronic studies
- ‡ required for chronic inhalation
- † In subchronic studies, examined only if indicated by signs of toxicity or target organ involvement
- † Org. weights required in subchronic and chronic studies
- †† Org. weight required for non-rodent studies

Macroscopic Pathology: No treatment-related effects were seen.

Organ weights: Organ weights were unaffected by treatment. In a previous study there were decreases in liver weights at 5, 10 and 20 mg/kg. In this study no changes in liver weights were apparent. Absolute heart weights in males at 5 mg/kg were decreased. Organ/body weight ratio were decreased in both 5 mg/kg and 20 mg/kg in males, while organ/brain weight ratios were decreased in males only at the 5 mg/kg dose level. This decrease can be seen on appended pages 4, 5 and 6, and was slight, was not seen in the last study at the same dose levels, and does not appear to be treatment-related.

Histopathology: No treatment-related effects were apparent.

Data Compilation

RULES FOR CALCULATIONS

appended pg 1 006730

The computer-generated values which appear in the tables represent the rounded-off results of the raw data values or of calculations which used the exact raw data values.

Group means were calculated according to the definition of any mean value using the individual values per animal or per cage and the number of animals or the number of cages.

Medians were calculated instead of mean values in case of discrete data like scores and counts.

The following data were recorded on-line: Clinical signs, food consumption, body weights, organ weights, necropsy including terminal body weights.

The following data were recorded on data sheets and transcribed for compilation and analysis: Visibility, mortality, ophthalmoscopy.

CALCULATION OF FOOD CONSUMPTION

The food consumption is calculated per cage and food consumption interval. It expresses the average food consumed per animal and per day for the cage considered and the observed food consumption interval.

$$\text{Formula (for each cage):} \quad FC = \frac{C}{\text{SUM (ND)}}$$

where FC = Food consumption (in g of food per animal and per day).

C = Food consumption measured over the consumption interval.

ND = Number of consumption days for one animal. The date of death if applicable is considered.

SUM (ND) = Total number of consumption days for all animals in the cage during the consumption interval.

CLINICAL SIGNS

The clinical signs are evaluated on a daily basis.

Daily evaluation.

- The individual data represent the maximum scores observed per animal and per day.
- The summary data show for each treatment group the median of the individual maximum scores, together with a code representing the percentage of animals affected.

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Statistical Analysis

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METHODS

Appended pg 2

The following statistical methods were used to analyze the body weights, food consumption, organ weights and clinical laboratory data

Univariate one-way analysis of variance was used to assess the significance of intergroup differences.

If the variables could be assumed to follow a normal distribution, the Dunnett-test (many to one t-test) based on a pooled variance estimate was applied for the comparison between the treated groups and the control groups.

The Steel-test (many-one rank test) was applied when the data could not be assumed to follow a normal distribution.

For the overall spontaneous mortality data, the Fisher's exact test for 2x2 tables was applied.

Group means were calculated for continuous data and medians were calculated for discrete data (scores) in the summary tables.

Individual values, means, standard deviations and statistics were rounded off before printing. For example, test statistics were calculated on the basis of exact values for means and pooled variances and then rounded off to two decimal places. Therefore, two groups may display the same printed means for a given parameter, yet display different test statistics values.

References:

- C.W. Dunnett: A Multiple Comparison Procedure for Comparing Several Treatments with a Control, J. Amer. Statist. Assoc. 50, 1096-121 (1955).
- R.G. Miller: Simultaneous Statistical Inference, Springer Verlag, New York (1981).
- R.A. Fisher: Statistical Methods for Research Workers, Oliver and Boyd, Edinburgh (1950).

For summary and results, see pp. 80 - 82.

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Appendix pg 3

**FOOD CONSUMPTION
(G/ANIMAL/DAY)
FEMALES**

SUMMARY

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TREATMENT		GROUP 1 0 MG/KG	GROUP 2 5 MG/KG	GROUP 3 20 MG/KG
DAYS 1-8	MEAN	19.3	19.6	17.7*
WEEKS 1/2	ST. DEV.	1.3	1.5	1.5
	N	10	10	10
DAYS 8-15	MEAN	19.7	20.0	18.8
WEEKS 2/3	ST. DEV.	1.4	1.3	1.7
	N	10	10	10
DAYS 15-22	MEAN	21.6	21.5	20.5
WEEKS 3/4	ST. DEV.	1.6	1.9	1.7
	N	10	10	10
DAYS 22-29	MEAN	23.2	23.3	21.5
WEEKS 4/5	ST. DEV.	1.7	1.7	2.1
	N	10	10	10
	MEAN	21.0	21.1	19.7

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* / ** : Dunnett-Test based on pooled variance significant at 5% (*) or 1% (**) level

ORGAN WEIGHTS (GRAM)
AFTER 4 WEEKS
MALES

Appended pg 4

SUMMARY

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		GROUP 1 0 MG/KG	GROUP 2 5 MG/KG	GROUP 3 20 MG/KG
BODY W.	MEAN ST. DEV. N	303.3 18.7 10	310.2 15.3 10	317.8 18.3 10
BRAIN	MEAN ST. DEV. N	1.96 0.06 10	1.94 0.07 10	1.98 0.07 10
HEART	MEAN ST. DEV. N	1.100 0.110 10	0.977 ** 0.065 10	1.020 0.089 10
LIVER	MEAN ST. DEV. N	8.56 0.55 10	8.43 0.68 10	8.91 0.82 10
KIDNEYS	MEAN ST. DEV. N	1.98 0.15 10	2.02 0.11 10	2.06 0.16 10
ADRENALS	MEAN ST. DEV. N	0.082 0.009 10	0.086 0.015 10	0.082 0.009 10
SPLEEN	MEAN ST. DEV. N	0.639 0.053 10	0.739 * 0.100 10	0.725 0.092 10
TESTES	MEAN ST. DEV. N	3.04 0.24 10	3.22 0.33 10	3.11 0.21 10

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* / ** : Dunnett-Test based on pooled variance significant at 5% (*) or 1% (**) level

ORGAN/BODY WEIGHT RATIOS SUMMARY
 AFTER 4 WEEKS
 MALES

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		GROUP 1 0 MG/KG	GROUP 2 5 MG/KG	006730	GROUP 3 20 MG/KG
BODY W (GRAM)	MEAN ST. DEV. N	303.3 18.7 10	310.2 15.3 10		317.8 18.3 10
BRAIN (Z)	MEAN ST. DEV. N	0.65 0.05 10	0.63 0.03 10		0.62 0.04 10
HEART (Z)	MEAN ST. DEV. N	0.364 0.043 10	0.315 ** 0.021 10		0.321 ** 0.025 10
LIVER (Z)	MEAN ST. DEV. N	2.82 0.16 10	2.72 0.19 10		2.80 0.15 10
KIDNEYS (Z)	MEAN ST. DEV. N	0.65 0.05 10	0.65 0.03 10		0.65 0.04 10
ADRENALS (Z)	MEAN ST. DEV. N	0.027 0.003 10	0.028 0.004 10		0.026 0.003 10
SPLEEN (Z)	MEAN ST. DEV. N	0.211 0.014 10	0.238 * 0.025 10		0.228 0.021 10
TESTES (Z)	MEAN ST. DEV. N	1.00 0.08 10	1.04 0.09 10		0.98 0.10 10

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* / ** : Dunnett-Test based on pooled variance significant at 5% (*) or 1% (**) level

ORGAN/BRAIN WEIGHT RATIOS SUMMARY
 AFTER 4 WEEKS
 MALES

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		GROUP 1 0 MG/KG	GROUP 2 5 MG/KG	GROUP 3 20 MG/KG
BRAIN (GRAM)	MEAN	1.96	1.94	1.98
	ST. DEV.	0.06	0.07	0.07
	N	10	10	10
HEART (Z)	MEAN	56.162	50.331	51.666
	ST. DEV.	6.705	3.934	5.424
	N	10	10	10
LIVER (Z)	MEAN	436.04	433.74	450.31
	ST. DEV.	28.07	28.55	37.71
	N	10	10	10
KIDNEYS (Z)	MEAN	100.80	104.20	104.02
	ST. DEV.	8.82	6.74	9.12
	N	10	10	10
ADRENALS (Z)	MEAN	4.150	4.458	4.170
	ST. DEV.	0.386	0.829	0.549
	N	10	10	10
SPLEEN (Z)	MEAN	32.566	38.021	36.722
	ST. DEV.	3.124	4.682	5.346
	N	10	10	10
TESTES (Z)	MEAN	154.79	165.75	157.33
	ST. DEV.	11.82	14.66	9.56
	N	10	10	10

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* / ** : Dunnett-Test based on pooled variance significant at 5% (*) or 1% (**) level