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DATA EVALUATION REPORT

STUDY TYPE: Inhalation study in rats.

TOX. CHEM. NO.: 889

ACCESSION NUMBER: 258996

MRID NO.: ?

TEST MATERIAL: HOE 38474 OH AT 210

SYNONYMS: Trifluralin

STUDY NUMBER(S): 5488

SPONSOR: Hoechst Aktiengesellschaft

TESTING FACILITY: Research Consulting Co Ltd. Itingen Switzerland

TITLE OF REPORT: 30-day repeated dose inhalation toxicity study
with HOE 38474OH A7 210 active ingredient (technical)

AUTHOR(S): L. Ullman

REPORT ISSUED: Feb. 12, 1982

CONCLUSIONS: Doses tested in nose-only inhalation study with exposure 6 hrs/day, 5 days/week were 100, 301 and 1006 mg/CBM. Effects were detected in group 4 showing signs of toxicity 6 hours after initial exposure. There was an increase in group 4 methemoglobin levels, however, the data were not presented to confirm or deny this statement. Total bilirubins were increased in the mid and high dose groups. The study stated that direct bilirubins were also elevated, but did not give the data to confirm this statement. Group 3 and 4 male and female absolute and relative liver weights were increased, and centrilobular hypertrophy of the liver was seen in high dose females and at all doses for males.

NOEL < 100 mg/CBM (LDT) based on centrilobular hypertrophy seen in males at all doses tested.

Classification: core-Supplementary, No macroscopic summary tables accompany the study text. Methemoglobin and direct bilirubin data are also missing from the study text.
Special Review Criteria (40 CFR 154.7)

A. MATERIALS:

1. Test compound: Trifluralin, Description red solid,
Batch # A201751, Purity 99.0%, contaminants: list in CBI appendix
Stated to be stable in original container at +25°C or -5°C for 2 years.

2. Test animals: Species: rats,
Strain: Wistar, KF_Han (outbred, SPF-quality)
Age: 10 weeks, at study initiation
Weight: Males- 175-180 gm., females- 171-177 gms.
Source: Kleintierfarm, Nadderin, AG4414 Fuellinsdorf, Switzerland

B. STUDY DESIGN:

1. Animal assignment

15/sex/group were assigned to the following test groups:
10 animals/sex/group were assigned to the main study which
ran for 30 days. 5 animals/sex/group were reserved for an
additional 14 days recovery period.

Test Group	Nominal air	Conc'n determined gravimetrically mg/CBMx/S.D.	Conc'n determined chemically mg/CBMx/S.D.
1 Cont.	600 l air/hr		
2 Low (LDT)	1.0 ml/hr	100 \pm 5	106 \pm 19
3 Mid (MDT)	2.0 ml/hr	301 \pm 8	307 \pm 56
4 High(HDT)	10.0 ml/hr	1006 \pm 23	1040 \pm 139
5 Solvent	10 ml acetone/hr		

2. Exposure

Exposure (nose only) was for 6 hours/day, 5 days/week for a total of 22 exposures.

3. Animals received food (Kliba 24/343/1 Batch 56/81) and water ad libitum.

4. Statistics - The procedures utilized are on appended page 1.

5. Quality assurance statement was not given.

C. METHODS AND RESULTS:

1. Observations

Animals were inspected daily for signs of toxicity and mortality. Appended pages 3 and 4 list the daily symptoms that were checked.

Results:

Toxicity: Group 4- after 6 hours on the first day of exposure and thereafter, showed slight dyspnoea and ruffled fur. These symptoms were continually seen just after exposure. No other groups showed signs of toxicity.

Mortality: No animals died during the duration of the test.

2. Body weight

Animals were weighed twice before starting the experiment, and twice weekly thereafter.

Results: Treated animal body weights were comparable to controls.

3. Food consumption and compound intake

Consumption was determined weekly throughout the entire test period. Food conversion was calculated according to the following formula:

$$\text{MFC} = \frac{\text{weekly food consumption}}{\text{body weight (gms)}} \times \frac{1000}{7}$$

Food consumption and conversion were measured only on 3 animals/sex/group.

Results: no effects were seen in food consumption. Group 4 females showed an increase in food conversion, However, the number of animals (3/group) makes this calculation useless.

4. Ophthalmological examinations

Performed once during the pretest phase and daily during the exposure and recovery periods.

Results: No treatment-related ocular changes were noted.

5. Blood was collected from 10 animals/sex/group after 30 days between 7:00 and 9:30 AM. Checked parameters were measured.

a. Clinical Chemistry

<u>X</u>	Electrolytes:	<u>X</u>	Other:
X	Calcium*		Albumin*
X	Chloride*	X	Blood creatinine*
	Magnesium*	X	Blood urea nitrogen*
	Phosphorous*		Cholesterol*
X	Potassium*		Globulins
X	Sodium*	X	Glucose*
	Enzymes	X	Total Bilirubin*
X	Alkaline phosphatase	X	Total Serum Protein*
	Cholinesterase#		Triglycerides
	Creatinine phosphokinase*°		Serum protein electrophoresis
X	Lactic acid dehydrogenase		
X	Serum alanine aminotransferase (also SGPT)*		
X	Serum aspartate aminotransferase (also SGOT)*		
	gamma glutamyl transferase		
	glutamate dehydrogenase		

* Required for subchronic and chronic studies

Should be required for OP

° Not required for subchronic studies

Results:

The statistical analyses in appendix O and the study text state that both total and direct bilirubin levels in group 4 females were significantly elevated. However, there are no data presented for direct bilirubin levels in the tables, or study text. No other clinical chemistry parameters appear to be affected by treatment.

Table I

females: Total Bilirubin \pm S.D.

1.	3.9 \pm 1.3
2.	5.1 \pm 2.1
3.	4.1 \pm 0.8
4.	6.3 \pm 1.1 **
5.	3.8 \pm 1.2

** = Significantly different from controls, $p < 0.01$

b. Hematology

X		X	
X	Hematocrit (HCT)	X	Leukocyte differential count
X	Hemoglobin (HGB)	X	Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)	X	Mean corpuscular HGB conc. (MCHC)
X	Erythrocyte count (RBC)	X	Mean corpuscular volume (MCV)
X	Platelet count	X	Reticulocyte count
	Blood clotting measurements	X	Heinz bodies
X	Thromboplastin time	X	Methemoglobin
X	Partial thromboplastin time		

Results: According to the study text there was a significant increase in methemoglobin formation in group 4 females. However, that information was not presented in the accompanying tables, and cannot be confirmed.

6. Urinalysis were not performed.

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 for all animals killed at termination of exposure and recovery period.

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

* 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

† Organ weights required in subchronic and chronic studies

†† Organ weight required for non-rodent studies

A- eye and contiguous Harderian glands examined microscopically

B- Examined microscopically with mainstem bronchi

C- examined microscopically with marrow

D- sciatic nerve

E- two lobes

Histopathological exams were done on all control and high dose animals, after 30 days of exposure. Also tissues of those animals of other groups where abnormal findings were noticed after macroscopic inspection were investigated. Lung, liver, spleen, bone marrow and kidneys were examined in rats of low, mid and recovery groups.

a. Organ weight

Absolute weights: There was a significant dose-response relationship for liver. In males and females of groups 3 and 4 liver weights were significantly different from controls.

Relative Weights (organ/body weights, organ/brain weights)
Liver to body weight and brain weight ratios were significantly increased in groups 3 and 4 males and females compared with controls, with a significant trend apparent for both sexes.

TABLE II

Liver Weights

Absolute weights \pm S.D.

Group	males	females
1	10.11 \pm 1.13	7.09 \pm 0.59
2	10.70 \pm 1.21	7.79 \pm 0.76
3	11.14 \pm 1.14*	8.39 \pm 0.72*
4	12.41 \pm 0.80*	9.36 \pm 1.52*

Liver/body weights \pm S.D.

Group	males	females
1	3.75 \pm 0.17	3.56 \pm 0.17
2	3.84 \pm 0.19	3.88 \pm 0.37
3	4.08 \pm 0.20*	4.02 \pm 0.24*
4	4.50 \pm 0.20*	4.53 \pm 0.49*

Liver/brain weights \pm S.D.

Group	males	females
1	539.40 \pm 60.33	391.30 \pm 42.34
2	553.74 \pm 71.65	431.46 \pm 39.44
3	557.03 \pm 54.39*	444.73 \pm 47.64*
4	651.04 \pm 40.03*	501.31 \pm 79.72*

b. Gross pathology

In the pathology summary report the study author stated that "in a few rats of the high dose group and of the solvent control group, small white foci were observed on the lungs. In addition a small number of minor lesions were encountered in various organs as described in the special part of this report". There are no macroscopic summary tables included in this report. This "special part" of the study text could not be found.

c. Microscopic pathology

1) Non-neoplastic

In the liver of both males and females, according to the study text, there was minimal to slight centrilobular hypertrophy characterized by increased homogeneity of cytoplasm and reduced basophilia in enlarged hepatocytes. Females showed a high dose effect, while in males, there was no NOEL (see table III). In males, the hepatocellular alteration increased in a dose-related manner.

In lungs, multifocal alveolar disruption with alveolar extensions were noted in all dose groups including controls.

Other microscopic changes seen could not be attributed to treatment.

TABLE III

Centrilobular Hypertrophy

Liver	group 1	2	3	4
Males	0	4	6	10
Females	0	0	0	7

2. Neoplastic: No neoplasms were detected during the study.

Discussion:

Effects were detected in group 4 showing signs of toxicity 6 hours after initial exposure. There was an increase in group 4 female methemoglobin levels, however, the data were not presented to confirm or deny this statement. Total bilirubins were increased in the mid and high dose groups. The study stated that direct bilirubins were also elevated, but did not give the data to confirm this statement. Group 3 and 4 male and female absolute and relative liver weights were increased, and centrilobular hypertrophy of the liver was seen in high dose females and at all doses for males.

NOEL < 100 mg/CBM (LDT) based on centrilobular hypertrophy seen in males at all doses tested.

Core Classification: supplementary

Page _____ is not included in this copy.

Pages 9 through 12 are not included.

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