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DATA EVALUATION REPORT

STUDY TYPE: 1-year dog study

TOX. CHEM. NO.: 573S

ACCESSION NUMBER: 263753

MRID NO.: ?

TEST MATERIAL: Harmony

SYNONYMS: DPX-M6316, H-15172-03

STUDY NUMBER(S): 201752

SPONSOR: Dupont de Nemours and Co.

TESTING FACILITY: Hazleton Laboratories, 9200 Leesburg Pike
Vienna Va, 22180

TITLE OF REPORT: One year feeding study in Dogs with H-15172-03

AUTHOR(S): N.N. Hamada

REPORT ISSUED: Jan 21, 1986

CONCLUSIONS: 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 decreased body weight and body weight gain in females after 22 weeks, the NOEL should be 750 ppm with an LEL of 7500 ppm.
Classification: core-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. Also no ophthalmological exams were performed.

A. MATERIALS:

1. Test compound: H-15172-03, Harmony
Description-off-white fluffy powder
Batch # 9760-1-3, 9926-89-1
Purity 98.2%, contaminants: given in text of study

2. Test animals: Species: dog, Strain:Beagles, Age: Adult,
Weight: Males-8.3-11.9 kg, females- 7.0-10.9 kg.
Source:Hazleton Research Animals Inc. Cumberland, Va.

B. STUDY DESIGN:

1. Animal assignment

Animals were assigned randomly to the following test groups:

Test Group	Dose in diet (ppm)	Main Study 12 months male	female
1 Cont.	0	5	5
2 Low (LDT)	50	5	5
3 Mid (MDT)	750	5	5
4 High(HDT)	7500	5	5

2. Diet preparation

Diet was prepared weekly and stored under refrigeration temperature. Samples of treated food were analyzed for stability and concentration at weeks 1, 31, and 52 from freshly prepared mixes, following room temp. exposures for 24 hours and following refrigeration for 10 days for stability. Samples were also taken at weeks 1, 10 and 52 from the top, middle and bottom of each mixture for potential homogeneity.

Results -
Results of the stability in test diet and concentrations at various sampling times were not provided in the text.

3. Animals received food and water ad libitum.

4. Statistics - Statistical treatment of study data are appended on pages 1 and 2.

5. Quality assurance was certified and a signed statement was enclosed with the study report.

C. METHODS AND RESULTS:

1. Observations

Animals were inspected twice daily for appearance, behavior, fecal elimination and for signs of toxicity and mortality.

Results: Mortality:
There were no deaths during the study.

Results: Observations:
No apparent treatment-related clinical observations were noted. Two males in group 2 and 1 female in group 4 developed mange and were treated with Mitaban.

2. Body weight

Animals were weighed weekly beginning 1 week prior to initiation of the study.

Results: Group 4 females showed decreased body weight and body weight gain from 22 weeks onward. There was a statistically significant decrease ($p > 0.05$) during weeks 0-26 and 0-39 but not at 0-52 weeks. See appended pages 3 and 4 for figures on body weight, and appended page 5 for a table detailing the decreases in body weight gain.

3. Food consumption and compound intake

Consumption was determined daily and mean daily diet consumption was calculated. Efficiency and compound intake were calculated from the consumption and body weight gain data.

Food consumption/Food Efficiency/Compound Intake

There was a significant increase in food consumption in group 4 males during weeks 1-26. No other significant changes were noted.
There were no significant changes in feed efficiency between groups. There was a slight depression in group 3 females, however, it was not significant, and isn't considered treatment-related.

4. Ophthalmological examinations were not performed.

Hematology

5. Blood was collected before treatment and at -3 and -1 weeks and during the study, weeks 4,8,13,26, 39, and 52 for hematology and clinical analysis from all animals. The CHECKED (X) parameters were examined.

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
X	Leukocyte and Erythrocyte morphology		

* Required for subchronic and chronic studies

Results: There were no treatment-related effects on hematological parameters. At 4 weeks there was an increase in all treated male and female groups in reticulocytes, but this did not persist and did not appear to be treatment-related.

b. Clinical Chemistry

X	Electrolytes:	X	Other:
X	Calcium*	X	Albumin*
	Chloride*	X	Blood creatinine*
	Magnesium	X	Blood urea nitrogen*
	Phosphorous*	X	Cholesterol*
X	Potassium*	X	Globulins
X	Sodium*	X	Glucose*
	Enzymes	X	Total Bilirubin*
X	Alkaline phosphatase	X	Total Serum Protein*
	Cholinesterase#		Triglycerides
	Creatinine phosphokinase*°	X	Direct Bilirubin
	Lactic acid dehydrogenase	X	Uric Acid
	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: Total bilirubin was decreased in both group 4 males and females at 52 weeks. It isn't clear if this is a compound-related phemonen.
There was an increase in glucose in group 3 and 4 males at 52 weeks and group 3 and 4 females at both 39 and 52 weeks. The increases were extremely slight and appeared to be more a function of a decrease in both male and female control levels, rather than a true treatment-related effect. The summary table data are appended for reference.
There were sporadic decreases in aspartate aminotransaminase in group 3 and 4 females at weeks 8, 13, and 52. These decreases do not appear to be consistent or substantial. These data are also appended for reference.

6. Urinalysis

Urine was collected from fasted animals at -3, -1 weeks, at 4, 8, 13, 26, 39 and 52 weeks. The CHECKED (X) parameters were examined.

X		X	
X	Appearance*	X	Glucose*
X	Volume*	X	Ketones*
X	Specific gravity*	X	Bilirubin*
X	pH	X	Blood*
X	Sediment (microscopic)*		Nitrate
X	Protein*	X	Urobilinogen
X	Osmolality	X	Reducing Substances

* Required for chronic studies
° Not required for subchronic studies

Results: There did not appear to be any treatment-related changes in the urinalysis parameters.

7. Sacrifice and Pathology -
All animals that died and that were sacrificed by exanguination under sodium thiamylal anaesthesia 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.

X		X		X	
	Digestive system		Cardiovasc./Hemat.		Neurologic
X	Tongue	X	.Aorta*	XX	.Brain*†
X	.Salivary glands*	X	.Heart*	X	Periph. nerve*#
X	.Esophagus*	X	.Bone marrow*	X	Spinal cord (2 levels)*#
X	.Stomach*	X	.Lymph nodes*	XX	.Pituitary*
X	.Duodenum*	X	.Spleen*	X	Eyes *#
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*†	XX	.Parathyroids*††
XX	.Liver*†	XX	Epididymides	XX	.Thyroids*††
XX	Gall bladder*#	X	Prostate		Other
X	.Pancreas*		Seminal vesicle		Bone*#
	Respiratory	XX	Ovaries*†	X	Skeletal muscle*#
X	.Trachea*	X	.Uterus*	X	Skin*#
X	.Lung*	X	Cervix	X	All gross lesions and masses*
	Nose°	X	Vagina		Tonsils
	Pharynx°				
	Larynx°				

* Required for subchronic and chronic studies
° Required for inhalation studies
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. Organ weight

Results:
These was a statistically significant increase ($p > 0.05$) in liver weights at the high dose in males, but it was not reflected in the liver/body weight ratios. The data are appended for reference. There was a statistically significant ($p > 0.05$) increase in thyroid/parathyroid-to-body weight ratios in the high dose females and a significant decrease ($p > 0.05$) in the same parameter in group 3 females. These data are also appended for reference. The significance of the group 3 findings is not clear. No other organ weight parameters were seen to change between treated and control animals.

b. Gross pathology

Results:

There were no treatment-related changes seen in the gross histopathology. All changes seen appeared in both controls and treated alike, and appeared to be associated with normal aging processes.

c. Microscopic pathology

Results:

Liver in the high dose females appeared to show a centrilobular hepatocellular clearing in 1/5, 0/5, 0/5, and 3/5 of the control low, medium, and high dose respectively. However, no other histopathology was evident and it is not clear if this is a treatment-related phenomen since no other effects in the liver were evident. No other treatment-related effects were seen during the histopathologic examination. All effects seen appeared to be associated with normal aging processes in the dog.

Discussion:

Based on the increased male liver weight at the high dose, along with the increased female thyroid/parathyroid-to-body weight ratio in the high dose and significant decreases in female body weight at several time periods in the high dose, the NOEL is 750 ppm with a LEL of 7500 ppm.

Several things are missing from the text which should be supplied by the registrant. These include, stability and concentration of test material in the animals diet at the various time periods given in the study text. It is not clear why Dupont did not have all the recommended clinical chemistry parameters such as chloride phosphorous and SGPT investigated, especially where there appeared to be some liver involvement. Dupont also didn't supply any ophthalmological examination information on the animals tested.

6

Harmony Reviews

Page _____ is not included in this copy.

Pages 7 through 15 are not included in this copy.

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___ Identity of product inert ingredients

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