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

MAY 12 1995 011546

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Subject: 5,5-Dimethylhydantoin. Review of Toxicology Data.
DP Barcode: D212481. Submission #: S482517.

To: Mark Wilhite/Tom Myers, PM# 51 Tox. Chem. No.: 114A
Reregistration Branch
Special Review and Reregistration Division (7508W)

From: Raymond K. Locke, Toxicologist Raymond K. Locke 4/20/95
Section II, Toxicology Branch I
Health Effects Division (7509C)

Thru: Joycelyn E. Stewart, Ph.D., Section Head 5/5/95
Section II, Toxicology Branch I
Health Effects Division (7509C) 5/5/95

Registrant: Lonza Inc.
Fair Lawn, NJ

Action Requested: Review toxicology data submitted to support reregistration of 5,5-dimethylhydantoin and indicate whether these data meet the requirements for a chronic (one-year) feeding study in the dogs (guideline 83-1b).

Conclusion: This study (MRID No.: 43553101) was adequately conducted and supports the reregistration of 5,5-dimethyl-hydantoin.

The data presented demonstrate that, under the study conditions, the study may be classified as follows:

MRID No.: 43553101. Chronic (One-Year) Toxicity (Dog). In this chronic (one-year) toxicity study, purebred beagle dogs, 4/sex/group, were administered 5,5-dimethylhydantoin (98.9% a.i.) in the diet at levels of 0, 4000, 12000, or 40000 ppm (corresponding to measured dose levels of 0, 120, 342, or 1506 mg/kg body wt./day for males and 0, 121, 414, and 1352 mg/kg body wt./day for females, respectively). All animals survived to scheduled sacrifice. At all doses tested, 5,5-dimethylhydantoin had no effect on body weight compared with control values at any time period. Statistically significant increases in the absolute weight of the adrenals and adrenal/body weight and adrenal/brain weight ratios were observed in the Group IV (40000 ppm) males; no other statistically significant effects on organ weight or

organ/body or brain weight ratios were observed. No treatment-related effects on food consumption were observed. No statistically significant effect on any of the hematology, clinical chemistry, or urinalysis parameters examined was observed at any dose level. Treatment-related clinical observations included discolored feces and oily coat in both males and females, with the latter observation most prevalent in males. Primarily in the mid- (Group III; 12000 ppm) and high- (Group IV; 40000 ppm) dose groups, gross necropsy revealed treatment-unrelated effects on the ear (nodule, scab, red color), lymph nodes (enlarged), skin (alopecia, red color), and spleen (red foci). Microscopic histopathology revealed hypertrophy of the adrenal cortex in all four males in the high-dose group (Group IV; 40000 ppm). This finding was not observed in males or females in the control group or mid- (Group III; 12000 ppm) or low- (Group II; 4000 ppm) dose treatment groups. The NOEL = 12000 ppm (342 mg/kg/day) and the LOEL = 40000 ppm (1506 mg/kg/day), based on enlarged adrenal glands in male dogs, shown by microscopic examiration to exhibit hypertrophy in the adrenal cortex.
Classification: Core-Guideline

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Reviewed by: Raymond K. Locke, Toxicologist Raymond K. Locke 4/4/95 83-1(b)
Section II, Tox. Branch I (7509C)
Secondary reviewer: Joycelyn E. Stewart, Ph.D. 5/4/95
Section Head, Section II, Tox. Branch I (7509C)

DATA EVALUATION REPORT

STUDY TYPE: Chronic (One-Year) Toxicity - Dog
TOX. CHEM NO: 114A
MRID NO.: 43553101

TEST MATERIAL: Dantoin®DMH (98.9% a.i.); Lot No.: K2432887; white crystalline solid

SYNONYMS: Dimethylhydantoin; 5,5-Dimethylhydantoin

STUDY NUMBER: 647-004

SPONSOR: Lonza Inc.
17-17 Route 208
Fair Lawn, NJ

TESTING FACILITY: International Research and Development Corporation
500 North Main Street
Mattawan, Michigan

TITLE OF REPORT: Evaluation of Dimethylhydantoin (DMH) in a One-Year Chronic Dietary Toxicity Study in Dogs

AUTHOR(S): Edwin I. Goldenthal, Ph.D.

REPORT ISSUED: January 6, 1995

EXECUTIVE SUMMARY: In this chronic (one-year) toxicity study, purebred beagle dogs, 4/sex/group, were administered 5,5-dimethylhydantoin (98.9% a.i.) in the diet at levels of 0, 4000, 12000, or 40000 ppm (corresponding to measured dose levels of 0, 120, 342, or 1506 mg/kg body wt./day for males and 0, 121, 414, and 1352 mg/kg body wt./day for females, respectively). All animals survived to scheduled sacrifice. At all doses tested, 5,5-dimethylhydantoin had no effect on body weight compared with control values at any time period. Statistically significant increases in the absolute weight of the adrenals and adrenal/body weight and adrenal/brain weight ratios were observed in the Group IV (40000 ppm) males; no other statistically significant effects on organ weight or organ to body or brain weight ratios were observed. Increases in food consumption during the latter half of the study (weeks 26-52) by Group IV (40000 ppm) males most likely resulted from inaccurate measurements due to digging in the food hoppers by two of the four dogs in this group; decreases in food consumption by females in all dose groups was neither dose- nor time-related and are not considered to be related to treatment with 5,5-dimethylhydantoin. Neither the apparent

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increases nor decreases in food consumption were reflected by corresponding changes in body weight. 5,5-Dimethylhydantoin, at all dose levels tested, had no statistically significant effect on any of the hematology, clinical chemistry, or urinalysis parameters examined for either males or females. Treatment-related clinical observations included discolored feces and oily coat in both males and females, with the latter observation most prevalent in males. Primarily in the mid- (Group III; 12000 ppm) and high- (Group IV; 40000 ppm) dose groups, gross necropsy revealed treatment-unrelated effects on the ear (nodule, scab, red color), lymph nodes (enlarged), skin (alopecia, red color), and spleen (red foci). Microscopic histopathology revealed hypertrophy of the adrenal cortex in all four males in the high-dose group (Group IV; 40000 ppm). This microscopic finding correlates with the increased weight of adrenals and adrenal weight to body and brain weight ratios found in this same treatment group. This finding was not observed in males or females in the control group or mid- (Group III; 12000 ppm) or low- (Group II; 4000 ppm) dose treatment groups. **The NOEL = 12000 ppm (342 mg/kg/day) and the LOEL = 40000 ppm (1506 mg/kg/day), based on enlarged adrenal glands in male dogs, shown by microscopic examination to exhibit hypertrophy in the adrenal cortex.**

Classification: Core-Guideline

Special Review Criteria (40 CFR 154.7) None met.

A. **MATERIALS:**

1. **Test compound:** Description - Dantoin®DMH; white crystalline powder; Lot # - K2432887, Purity - 98.9%.

2. **Test animals:** Species: Dog, Strain: purebred beagle, Age. 5 months, Weight: Males: 8.8-11.6 kg; Females: 6.7-8.3 kg, Source: Marshall Farms, North Rose, New York.

B. **STUDY DESIGN:**

1. **Animal assignment**

Animals were assigned, on the basis of prior weight determinations and physical examinations aimed at yielding healthy treatment groups having similar body weight means and standard deviations, to the test groups described in the following Table I:

Table I: Test Groups and Dose Levels Employed in Study

Test Group	Dose in diet (ppm)	Main Study (12 months) male	female	Actual Dose Delivered (mg/kg/day)[a] male	female
1 Control	0	4	4	0.0	0.0
2 Low (LDT)	4,000	4	4	119.9	120.6
3 Mid (MDT)	12,000	4	4	341.6	413.6
4 High (HDT)	40,000	4	4	1506.2	1352.1

[a]Data extracted from page 24 of this submission (MRID No.: 43553101)

Dietary dose levels for the definitive study (MRID No.: 43553101) were selected on the basis of a dose range-finding study, not submitted separately and only summarized in this submission (MRID No.: 43553101). In the range-finding study, 5,5-dimethylhydantoin was administered in the diet at levels of 1200, 4000, 12000, and 40000 ppm. The number and sex of the purebred beagle dogs used this range-finding are not specified, nor is the length of the exposure period. As there were no clearly treatment-related effects observed in the range-finding study, a dietary level of 40000 ppm was selected as the high dose for use in the definitive study (MRID No.: 43553101). The 40000 ppm dietary level was also selected as the high-dose level because this level is theoretically equivalent to a dose level of 1.0 g/kg body wt./day, which is the "limit dose" for chronic studies. The 12000 ppm and 4000 ppm dietary levels were selected for inclusion in the definitive study (MRID No.: 43553101) to provide doses potentially resulting in intermediate effects and no effects, respectively, if longer-term exposure to the high-dose level (40000 ppm) elicited effects.

2. **Diet preparation**

Diet (Certified Canine Chow® #5007, Ralston Purina Company, St. Louis, Mo.; with added test substance) was prepared fresh each week and stored at room temperature. Samples of treated food were collected weekly; samples from every fourth week were analyzed for concentration, and the remaining samples were frozen for possible future analysis. Prior to study start, the homogeneity of test diets at test substance concentrations of 4,000 and 40,000 ppm was examined. After diet preparation, duplicate samples were taken from the top, bottom, and middle of the blender, and the samples were analyzed for test substance concentration. The diets were then placed in plastic storage bags and stored at room temperature for 14 days. At this time, duplicate samples of the diets were taken form the top, bottom, and middle of the bags, and the

sample analyzed for test substance content. Test substance concentration was determined using a liquid chromatographic procedure.

Results - Test diets were shown to be both homogeneous and stable over a 14-day period, and the concentrations achieved were within ±4% of target. When the six samples (duplicates from top, bottom, and middle of blender) of the two diets were analyzed for homogeneity immediately after preparation, the results shown in the following Table II were obtained. Table II also presents the results when the six samples (duplicates from the top, bottom, and middle of diets stored in plastic bags) were analyzed for the two diets after 14 days of storage at room temperature.

Table II: Homogeneity, Concentration, and Stability of Test Diets[a]

Dietary concentration (ppm)	Range of ppm found	Mean and standard deviation	Percent of target concentration
Analysis Immediately After Preparation:			
4000	3710-4160	3930±175	98
40000	38400-44300	40400±2190	101
Analysis Following Two Weeks of Storage at Room Temperature:			
4000	3910-4880	4230±352	106
40000	37200-44300	40600±2820	102

[a]Data extracted from page 21 of this submission (MRID: 43553101).

3. Animals received food for a three-hour period each day (usually between 8-11 a.m.) and water ad libitum.

4. **Statistical Analyses** - The following procedures were utilized in analyzing the numerical data: body and organ weights (and organ to body weight and brain weight ratios), food consumption values, and clinical parameters were analyzed using one-way analysis of variance, followed (if indicated) by Barlett's test (as described by Steel and Torrie), and appropriate pairwise comparisons. If non-parametric statistics were required, the rank transformation methods of Conover and Iman were used. Statistical tests were conducted at the 0.05 level unless otherwise indicated.

5. A signed quality assurance statement was included in the study.

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C. METHODS AND RESULTS:

1. Clinical Observations:

Physical examinations were conducted on each dog before study initiation, at 3, 6, and 9 months on study, and prior to study termination. An assessment of general physical condition, and examination of the head, neck, thorax, abdomen, external reproductive organs, skin, and extremities were included, as was auscultation of the thoracic cavity and respiratory tract and palpation of the thoracic cage and abdomen.

Following study initiation, animals were inspected at least twice daily for signs of toxicity and mortality, and detailed clinical examinations were conducted at least once weekly.

The results of the physical examinations at all time periods revealed only a prevalence of dermatitis and related skin effects (erythema) in all treatment groups at various body sites. Since these effects were observed in controls and all treatment groups at various time periods, they are not considered to be related to treatment.

All animals survived to study termination. Treatment-related clinical signs included discolored feces in both males and females and oily coat (most pronounced in males). Although injection of the sclera of the eye was frequently observed in both males and females at all dose levels, the incidence in animals receiving 5,5-dimethyl-hydantoin was no greater than that of respective control animals. Therefore, this ocular effect is not regarded as treatment-related, and this conclusion is confirmed by the lack of treatment-related findings from ophthalmological examination. Incidences of representative clinical findings are presented in the following Table III:

Table III: Incidences of Representative Clinical Findings in Dogs Ingesting Food Containing 5,5-Dimethylhydantoin for 90 Days[a]

Sex and Dose	Discolored Feces	Oily Coat	Injected Sclera of Eye(s)
0 ppm (Control)			
Males	0/4	0/4	3/4
Females	1/4	1/4	4/4
400 ppm (LDT)			
Males	3/4	0/4	3/4
Females	1/4	0/4	3/4

1200 ppm (MDT)			
Males	3/4	4/4	3/4
Females	3/4	2/4	4/4
40000 ppm (HDT)			
Males	2/4	4/4	4/4
Females	2/4	0/4	4/4

[a]Data extracted from Appendix D, pages 124-155 of this submission (MRID No.: 43553101).

2. **Body weight**

Animals were weighed prior to study initiation, weekly during the study, and prior to sacrifice.

5,5-Dimethylhydantoin, at all doses tested, had no statistically significant effect on body weight throughout the duration of this one-year study. Slight decreases in body weight (5% of control value or less) were observed in males and females in the high-dose (40000 ppm; Group IV) group, but these decreases were never statistically significant and occurred during the last nine months of the study. Representative body weight data are presented in the following Table IV:

able IV. Representative Group Mean Body Weights (Kg) of Dogs Receiving 5,5-Dimethylhydantoin in the Diet for a One-Year Period[a]

Dietary Concentration (ppm)	Pretest	Week 13	Week 26	Week 39	Week 52
Males					
0 (Group I; Control)	10.0	11.3 (+13.0)[b]	12.2 (+22.0)	13.1 (+31.0)	13.6 (+36.0)
4000 (Group II; LDT)	10.2	11.7 (+14.7)	12.7 (+24.5)	12.7 (+24.5)	13.4 (+31.4)
12000 (Group III; MDT)	10.1	11.8 (+16.8)	13.0 (+28.7)	13.1 (+29.7)	13.7 (+35.6)
40000 (Group IV; HDT)	9.7	11.0 (+13.4)	12.2 (+25.8)	12.2 (+25.8)	12.6 (+29.9)
Females					
0 (Group I; Control)	7.8	8.9 (+14.1	9.8 (+25.6)	10.0 (+28.2)	10.6 (+35.9)
4000 (Group II; LDT)	7.6	9.1 (+19.7)	10.2 (+34.2)	10.1 (+32.9)	11.3 (+48.7)

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12000 (Group III; MDT)	7.6	8.6 (+13.2)	9.1 (+19.7)	[illegible] (+2[illegible])	[illegible].0 [illegible].6)
40000 (Group IV; HDT)	7.6	8.1 (+6.6)	9.4 (+23.7)	9.2 (+21.1)	10.3 (+35.5)

)ata extracted from page 23 of this submission (MRID No.: 43553101). 'igures in parentheses represent the percent difference from pretest alue.

3. **Food consumption and compound intake**

Individual food consumption was determined weekly and mean weekly diet consumption was calculated. Test substance intake was calculated from the consumption and bod, weight gain data.

Administration of 5,5-dimethylhydantoin in the diet had little, if any, effect on the food consumption of males at any dose level. Food consumption increases of males in the high-dose (40000 ppm; Group IV) during weeks 40 (176% control value; $p \leq 0.01$), 45 (166% control value; $p \leq 0.01$) and 46 (170 % control value; $p \leq 0.01$) are best explained by inaccurate measurements due to spillage of the food from the hoppers caused by digging by two of the dogs in this treatment group. No other statistically significant changes in food consumption by males were observed.

On the other hand, females ingesting diets containing 5,5-dimethylhydantoin exhibited many statistically significant ($p \leq 0.05$ or 0.01) decreases (68-84% control value) in food consumption in all dose groups in a cyclical 6-7 week time interval, starting with week 13 on test. These decreases in food consumption appear to be related neither to time-on-test nor to concentration of the test substance in the diet, but seem to occur at approximately 6-7 week intervals in all test groups with approximately the same degree of decrease in food consumption. Therefore, these decreases in food consumption are not considered to be treatment-related. It should be noted that these cyclic decreases in food consumption observed in the females were not reflected in statistically significant body weight changes.

Consumption of 5,5-dimethylhydantoin on a mg/kg/day basis was calculated from the weekly body weight and food consumption data. These calculated values have been presented in Table I.

4. **Ophthalmological examination**

Examinations were performed on each dog prior to study initiation and during the last week of the study (week 52). No treatment-related ophthalmological effects were observed.

5. **Blood was collected** from all animals, following overnight withdrawal of both food and water, before treatment and at study termination (52 weeks) for hematology and clinical analysis . The CHECKED (X) parameters were examined.

a. **Hematology**

X		X	
X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)
X	Platelet count*	X	Reticulocyte count
	Blood clotting measurements		
	(Thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

* Required for subchronic and chronic studies

Results - 5,5-Dimethylhydantoin, at all dose levels tested, had no statistically significant effect on any of the hematology parameters examined for either males or females.

b. **Clinical Chemistry**

X		X	
	Electrolytes:		Other:
X	Calcium*	X	Albumin*
X	Chloride*	X	Blood creatinine*
	Magnesium*	X	Blood urea nitrogen*
X	Phosphorous*	X	Cholesterol*
X	Potassium*	X	Globulins
X	Sodium*	X	Glucose*
	Enzymes		Total bilirubin
X	Alkaline phosphatase (ALK)	X	Total serum Protein (TP)*
	Cholinesterase (ChE)#		Triglycerides
X	Creatinine phosphokinase*^		Serum protein electrophores
	Lactic acid dehydrogenase (LAD)		
X	Serum alanine aminotransferase (also SGPT)*		
X	Serum aspartate aminotransferase (also SGOT)*		
	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase		

* Required for subchronic and chronic studies
# Should be required for OP
^ Not required for subchronic studies

Results - 5,5-Dimethylhydantoin, at all doses tested, had no statistically significant treatment-related effect on any of the clinical chemistry parameters examined. The only statistically significant differences from control values were: 1) 67% of control value pre-test alkaline phosphatase activity in high-dose (40000 ppm; Group IV) males (values no different from control values at 6 months and 12 months); 2) 80% of control value terminal (12-month) creatinine concentration in mid-dose (12000 ppm; Group III) females (values no different from control values for females in any other treatment group at any time period); and 3) 92% of control value 6-month total protein in low-dose (4000 ppm; Group II) females (no differences from control value observed at 12 months). Since these statistically significant changes were not dose- or time-related, they are not considered to be related to treatment with 5,5-dimethylhydantoin.

6. **Urinalysis^**

Urine was collected from fasted animals prior to study initiation, at 6 months on test, and at study termination (12 months). 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)*		Nitrite
X	Protein*		Urobilinogen
			Cells

^Not required for subc[illegible]
* Required for chroni[illegible]s

Results - 5,5-D[illegible]ylhydanto[illegible]l doses tested, caused no treat[illegible]ally significant effect on any u[illegible]xamined in any animal from any treatme[illegible]stically significant differences from [illegible]re observed for any dose group.

7. **Sacrifice and Patholo[illegible]**

All animals that died and [illegible]hat were sacrificed on schedule were subject to gross path[illegible]logical examination and the CHECKED (X) tissues [illegible]ollected for histological examination. The [illegible]ns, in addition, were weighed.

X	Digestive system	X	Cardiovasc./Hemat.	X	Neurologic
	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*	XX	Pituitary*
X	Duodenum*	X	Spleen	X	Eyes (optic n.)*#
X	Jejunum*	X	Thymus*		Glandular
X	Ileum*		Urogenital	XX	Adrenal gland*
X	Cecum*	XX	Kidneys*+		Lacrimal gland#
X	Colon*	X	Urinary bladder*	X	Mammary gland*#
X	Rectum*	XX	Testes*+	XX	Parathyroids*++
XX	Liver *+	XX	Epididymides	XX	Thyroids*++
X	Gall bladder*	X	Prostate		Other
X	Pancreas*		Seminal vesicle	X	Bone*#
	Respiratory	XX	Ovaries*+	X	Skeletal muscle*#
X	Trachea*		Uterus*	X	Skin*#
X	Lung*			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 weight required in subchronic and chronic studies.
++ Organ weight required for non-rodent studies.

a. **Organ weight** - The only effects elicited by 5,5-dimethylhydantoin with respect to absolute organ weights and organ weight to body weight or brain weight ratios were found in high-dose (40000 ppm; Group IV, males and consisted of: 1) increased (but not statistically significantly) absolute right (137% control value) and left (124% control value) adrenal weights; 2) increased left adrenal/body wt. ratio (138% control value; $p \leq 0.01$) and left adrenal/brain wt. ratio (130% control value; no p); 3) increased right adrenal/body wt. ratio (149% control value; $p \leq 0.01$) and right adrenal/brain wt. ratio (142% of control value; $p \leq 0.05$). No other statistically significant differences from control values were noted in any animal from any treatment group.

b. **Gross pathology** - Potentially treatment-related macroscopic findings were observed in the ear, skin, spleen, and lymph nodes. Although effects were rarely observed in control animals, in [illegible] cases evidence for

dose-response was limited. Representative macroscopic findings are presented in the following Table V:

Table V: Incidence of Representative Macroscopic Observations in Dogs Receiving 5,5-Dimethylhydantoin in the Diet for a One-Year Peri

Dose Group (ppm)	0	4000	12000	400C
Males				
Ear	(0)[b]	(0)	(2)	(2)
Normal	0	0	1	0
Nodule	0	0	1	1
Scab	0	0	0	1
Red Color	0	0	0	1
Lymph Nodes (Enlarged)	(0)	(0)	(0)	(2)
Mesenteric	0	0	0	2
Lymph Nodes (Enlarged)	(0)	(0)	(0)	(1)
Tracheobronchial	0	0	0	1
Skin	(1)	(2)	(4)	(4)
Normal	1	2	2	2
Alopecia	0	0	0	1
Red Color	0	0	2	1
Spleen	(0)	(1)	(0)	(2)
Red foci	0	1	0	2
Females				
Ear	(0)	(1)	(0)	(1)
Fistula	0	1	0	0
Scar	0	0	0	1
Lymph Nodes (Enlarged)	(0)	(0)	(1)	(0)
Tracheobronchial	0	0	1	0
Skin	(2)	(2)	(3)	(4)
Normal	1	2	1	3
Nodule	0	0	2	0
Alopecia	1	0	0	1
Spleen	(1)	(0)	(1)	(1)
Red Foci	1	0	1	1

[b]Data extracted from pages 77-82 of this submission (MRID No.: 43553101)

c. **Microscopic pathology** - Representative microscopic findings are presented in the following Table VI:

Table VI: Representative Microscopic Findings in Dogs Receiving 5,5-Dimethylhydantoin in the Diet for One Year[a]

Dose Group (ppm)	0	4000	12000	40000
	Males			
Adrenal Gland (Cortex)	(4)[b]	(4)	(4)	(4)
Normal	4	3	4	0
Vacuolar change, mild	0	1	0	0
Hypertrophy	0	0	0	4
Trace	0	0	0	2
Mild	0	0	0	2
Ear	(0)	(0)	(1)	(2)
Acanthosis	0	0	1	1
Mild	0	0	0	1
Moderate	0	0	1	0
Histiocytoma	0	0	0	1
Inflammation (Trace)	0	0	1	1
Liver	(4)	(4)	(4)	(4)
Normal	4	4	3	3
Hemangioma	0	0	1	0
Infiltration (Trace)	0	0	0	1
Kidney	(4)	(4)	(4)	(4)
Normal	0	0	0	1
Mineralization (Trace)	4	4	4	3
Nephritis (Interstitial, Mild)	0	1	0	0
Congestion (Mild)	0	1	0	0
Parathyroid Gland	(4)	(4)	(4)	(4)
Normal	3	3	2	3
Cyst	1	1	2	1
Trace	1	0	2	1
Mild	0	1	0	0
Mineralization (Trace)	1	0	0	0
Pituitary Gland	(4)	(4)	(4)	(4)
Normal	3	3	4	4
Cyst	1	1	0	0
Mild	0	1	0	0
Moderate	1	0	0	0
Lymph Node, Mandibular	(4)	(4)	(4)	(4)
Normal	3	1	3	2
Brown Pigment	1	3	1	2
Trace	0	2	1	2
Mild	1	1	0	0

Skin	(4)	(4)	(4)	(4)
Normal	4	4	2	2
Acanthosis (Mild)	0	0	2	2
Hyperkeratosis (Mild)	0	0	0	1
Inflammation (Trace)	0	0	0	2
Spleen	(4)	(4)	(4)	(4)
Normal	4	2	4	2
Congestion	0	2	0	2
Trace	0	1	0	1
Mild	0	0	0	1
Moderate	0	1	0	0
Females				
Ear	(0)	(1)	(0)	(1)
Normal	0	1	0	0
Acanthosis (Trace)	0	0	0	1
Liver	(4)	(4)	(4)	(4)
Normal	4	3	2	3
Hypertrophy	0	1	1	1
Trace	0	1	1	0
Mild	0	0	0	1
Infiltration (Mononuclear Cell, Trace)	0	0	1	0
Mammary Gland	(4)	(4)	(4)	(4)
Normal	3	1	2	1
Hyperplasia	1	3	2	3
Trace	0	0	1	0
Mild	1	1	1	2
Moderate	0	2	0	1
Mineralization (Trace)	0	0	0	1
Parathyroid Gland	(4)	(4)	(4)	(4)
Normal	4	3	2	3
Cyst (Trace)	0	1	2	1
Pituitary Gland	(4)	(4)	(4)	(4)
Normal	3	3	2	2
Cyst	1	1	2	2
Trace	0	1	1	0
Mild	0	0	0	1
Moderate	0	0	1	1
Severe	1	0	0	0
Kidney	(4)	(4)	(4)	(4)
Mineralization	4	4	4	4
Trace	4	4	3	4
Mild	0	0	1	0

Uterus	(4)	(4)	(4)	(4)
Normal	3	2	2	2
Hydrometra (Mild)	0	1	0	0
Hyperplasia (Glandular, Mild)	1	2	2	2
Spleen	(4)	(4)	(4)	(4)
Normal	3	3	2	2
Congestion	1	1	2	2
Trace	1	0	0	0
Mild	0	0	2	1
Moderate	0	1	0	1

[a]Data extracted from pages 93-108 of this submission (MRID No.: 43553101).
[b]Number in parentheses indicates the number of animals examined.

1) **Non-neoplastic** - Confirming the increase in absolute and relative (to body and brain weight) weight of the adrenal glands in males (4/4) of the high-dose (Group IV; 40000 ppm), microscopic examination revealed hypertrophy of the adrenal cortex in these animals. This finding was not observed in males or females in the control group or mid- (Group III; 12000 ppm) or low- (Group II; 4000 ppm) treatment groups. Treatment-unrelated (no dose-response apparent) findings included: 1) hyperplasia of the uterus (seen in controls and across all dose groups); 2) congestion of the spleen (seen in female controls and across all dose groups in males and females); 3) pituitary and parathyroid cysts (seen in controls and various dose groups); 4) brown pigment in mandibular lymph nodes (all males in control and treatment groups); and 5) mineralization of the renal medulla (all control and treatment groups).

2) **Neoplastic** - As shown in Table VI, one of the high-dose (40000 ppm; Group IV) males exhibited an histiocytoma of the ear, while one mid-dose (12000 ppm; Group III) male exhibited an hemangioma of the liver. Neither of these tumors were observed in other animals at any level of 5,5-dimethylhydantoin tested. According to Melba S. Morrow, D.V.M., Toxicology Branch I, neither of these tumors is uncommon in purebred beagle dogs. Therefore, in view of the available toxicological data, the occurrence of these two tumors is not considered to be related to treatment with 5,5-dimethyl-hydantoin.

D. **DISCUSSION:**

Overall, this study is well planned and executed; is also reported in a very detailed manner. Therefore, this study is classified as Core-Guideline.