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WASHINGTON, D.C. 20460

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HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361
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OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: 1-Bromo-3-chloro-5,5-dimethylhydantoin: Review of Toxicology Data

DP Barcode No. D225125 Rereg. Case No. 3055
Submission No. S503664 P.C. Code No. 006315
Tox. Chem. No. 114A

TO: Kathleen Depukat PM# 51
Reregistration Branch
Special Review and Reregistration Division (7508W)

FROM: Raymond K. Locke, Toxicologist Raymond K. Locke 5/17/96
Section II, Toxicology Branch I
Health Effects Division (7509C)

THRU: Joycelyn E. Stewart, Ph.D., Section Head 6/3/96
Section II, Toxicology Branch I
Health Effects Division (7509C) KB 7/15/96

Registrant: Lonza, Inc.
Fair Lawn, NJ

Action Requested: Review toxicology data (MRID No.: 43972101) submitted to support reregistration of 1-bromo-3-chloro-5,5-dimethylhydantoin and related pesticides (P.C. Codes: 006371; 02850 abd 128826).

Conclusion: This study was adequately conducted and supports the reregistration of the above-listed pesticides.

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

MRID No.: 43972101. Non-guideline dose range-finding subchronic (8 week) toxicity study in the dog. In a non-guideline subchronic dose range-finding toxicity study (MRID 43972101) for a one-year dog chronic toxicity study (MRID 43553101), 5,5-dimethylhydantoin (DMH; 99.8% a.i.) was orally administered to male and female purebred bea dogs (2/sex/dose) in the diet at analytically determined dose level of 0, 1140, 3820, 11550, or 39600 ppm (corresponding to 0, 32, 170, 509, or 1598 mg/kg/day in males and 0, 41, 558, or 1650 mg/kg/day i females) for a period of eight weeks.

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DMH, at all dose levels tested, elicited no compound-related effects on mortality, clinical signs, body weight, organ weights, organ/body weight or organ/brain weight ratios, food consumption, hematology, clinical chemistry, organ weights, or gross and histologic pathology. **The LOEL is greater than 39600 ppm (HDT) in the diet, based on the lack of any observed adverse effects. The NOEL is equal to or greate than 39600 ppm (HDT) in the diet.**

This subchronic (8-week) dose range-finding toxicity study is classified supplementary (not upgradable) and does not satisfy the guideline requirement for a subchronic oral study (82-1b) in the non-rodent (dog); however, it is fully satisfactory for its intended purpose of setting dose levels for a one-year chronic toxicity study (83-1b) in the dog.

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P.C. CODE: 006315 - 5,5-Dimethylhydantoin

FILE LAST PRINTED:

CITATION	MATERIAL	ACCESSION/ MRID. NO.	RESULTS	TOX CAT	CORE GRADE/ DOCUMENT #
Non-Guideline 82-1(b) Subchronic (8-week) Toxicity Species: Dog MPI Research, Mattawan, MI 647-002; 2/14/96	Dimethylhydantoin (DMH; 99.8% a.i.) (5,5-Dimethylhydantoin; 99.8% a.i.) Related CASWELL Nos.: 287AAA; 306; 309C	43972101	In a non-guideline subchronic dose range-finding toxicity study (MRID 43972101) for a one-year dog chronic toxicity study (MRID 43553101), 5,5-dimethylhydantoin (DMH; 99.8% a.i.) was orally administered to male and female purebred beagle dogs (2/sex/dose) in the diet at analytically determined dose levels of 0, 1140, 3820, 11550, or 39600 ppm (corresponding to 0, 32, 170, 509, or 1598 mg/kg/day in males and 0, 41, 558, or 1650 mg/kg/day in females) for a period of eight weeks. DMH, at all dose levels tested, elicited no compound-related effects on mortality, clinical signs, body weight, organ weights, organ/body weight or organ/brain weight ratios, food consumption, hematology, clinical chemistry, organ weights, or gross and histologic pathology. **The LOEL is greater than 39600 ppm (HDT) in the diet, based on the lack of any observed adverse effects. The NOEL is equal to or greater than 39600 ppm (HDT) in the diet.** This subchronic (8-week) dose range-finding toxicity study is classified supplementary (not upgradable) and does not satisfy the guideline requirement for a subchronic oral study (82-1b) in the non-rodent (dog); however, it is fully satisfactory for its intended purpose of setting dose levels for a one-year chronic toxicity study (83-1b) in the dog.	--	Supplementary (Dose Range-Finding Study)

EPA Reviewer: Raymond K. Locke Raymond K. Locke Date 5/17/96
Review Section 2, Toxicology Branch I (7509C)
EPA Secondary Reviewer: Joycelyn E. Stewart, Ph.D. JES Date 6/4/96
Section Head, Review Section 2, Toxicology Branch I (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Subchronic Oral Toxicity (Feeding) - Dog; Range-Finding Study for Chronic Toxicity - Dog (MRID No.: 43553101) OPPTS 870.4100 [§83-1b]

DP BARCODE: D225125 SUBMISSION CODE: S503664
P.C. CODE: 006315 TOX. CHEM. NO.: 114A

TEST MATERIAL (PURITY): Dimethylhydantoin (DMH; 99.8% a.i.)

SYNONYMS: 5,5-Dimethylhydantoin

CITATION: Goldenthal, E. (1996). Evaluation of dimethylhydantoin in an eight-week dietary toxicity study in dogs. MPI Research, Mattawan, MI. Laboratory report number: 647-002, February 14, 1996. MRID 43972101. Unpublished.

SPONSOR: Lonza, Inc.
Fair Lawn, NJ

EXECUTIVE SUMMARY:

In a non-guideline subchronic dose range-finding toxicity study (MRID 43972101) for a one-year dog chronic toxicity study (MRID 43553101), 5,5-dimethylhydantoin (DMH; 99.8% a.i.) was orally administered to male and female purebred beagle dogs (2/sex/dose) in the diet at analytically determined dose levels of 0, 1140, 3820, 11550, or 39600 ppm (corresponding to 0, 32, 170, 509, or 1598 mg/kg/day in males and 0, 41, 558, or 1650 mg/kg/day in females) for a period of eight weeks.

DMH, at all dose levels tested, elicited no compound-related effects on mortality, clinical signs, body weight, organ weights, organ/body weight or organ/brain weight ratios, food consumption, hematology, clinical chemistry, organ weights, or gross and histologic pathology. **The LOEL is greater than 39600 ppm (HDT) in the diet, based on the lack of any observed adverse effects. The NOEL is equal to or greater than 39600 ppm (HDT) in the diet.**

This subchronic (8-week) dose range-finding toxicity study is classified supplementary (not upgradable) and does not satisfy the guideline requirement for a subchronic oral study (82-1b) in the non-rodent (dog); however, it is fully satisfactory for its intended purpose of setting dose levels for a one-year chronic toxicity study (83-1b) in the dog.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: Dimethylhydantoin (DMH)
   Description: White crystalline powder
   Lot/Batch #: NO432543
   Purity: 99.8 % a.i.
   Stability of compound: Stable under conditions of duration of study and storage conditions
   CAS #: Not given

2. Vehicle and/or positive control: No vehicle or positive control was used in this study.

3. Test animals: Species: Dog
   Strain: Pure-bred beagle
   Age and weight at study initiation: 4 to 4-1/2 months; males: 8.1-10.2 kg; females: 6.0-8.3 kg
   Source: Marshall Research Animals, North Rose, NY
   Housing: Individually housed in stainless steel cages
   Diet: Certified Canine Chow® #5007, Purina Mills, ad libitum
   Water: Tap water, ad libitum
   Environmental conditions:
   Temperature: 68-78°F
   Humidity: 30-70%
   Air changes: Not specified
   Photoperiod: 12/12 hrs of dark/light
   Acclimation period: One month

B. STUDY DESIGN:

1. In life dates - start: 8/23/91 end: 10/18/91 or 10/21/91

2. Animal assignment

   Animals were assigned randomly to the test groups shown in Table 1 with the objective of having study groups of similar body weight means. Prior to study initiation, all animals underwent complete physical examinations, and any animal in which disease was found or which did not exhibit normal weigh gain during the acclimation period was not placed on test.

TABLE 1: Assignment of Animals to Study Groups[a]

Test Group	Conc. in Diet (ppm)[b]	Dose to Animal (mg/kg/day)[c]	Males Assigned	Females Assigned
Control	0	0	2	2
Low (LDT)	1140	32 M[d] 41 F	2	2
Low-Mid (LMDT)	3820	170 M 179 F	2	2
High-Mid (HMDT)	11550	509 M 558 F	2	2
High (HDT)	39600	1598 M 1650 F	2	2

[a]Data extracted from pages 12, 17, and 19 of this submission (MRI No.: 43972101).
[b]Analytically determined values.
[c]Values determined from body weight and feed consumption figures.
[d]M = males; F = females.

3. Diet preparation and analysis

Diet was prepared weekly by mixing appropriate amounts of test substance with Purina Certified Canine Chow #5007 and was stored at room temperature. Actual concentration of test substance in the diets was tested at four-week intervals. During the study, samples of treated food were analyzed for stability and concentration in conjunction with the one-year chronic toxicity study in dogs (MRID No.: 43553101). After sampling for concentration of the test substance at 4-week intervals, 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 from the top, bottom, and middle of the bags, and the composite (mixed) samples analyzed for test substance content. Test substance concentration was determined using a liquid chromatographic procedure with an authentic standard of DMH.

Results - Homogeneity Analysis: "Confirmed*"
Stability Analysis: "Confirmed*"
Concentration Analysis: 95-99%

*No actual figures are given in this submission (MRID No.: 43972101), but the homogeneity and stability of test diets used in the one-year study (MRID No. 43553101) containing the same dosage levels as used in this range-finding study (MRID No.: 43972101) were adequate.

The analytical data indicate that the mixing procedure was adequate and that the variance between nominal and actual dosage to the animals was acceptable.

4. Statistics - Since there were only two dogs in each study group, no statistical analyses were conducted.

C. METHODS:

1. Observations:

Animals were inspected twice daily for signs of toxicity and mortality.

2. Body weight

Animals were weighed prior to study initiation, weekly while on test, and prior to sacrifice.

3. Food consumption and compound intake

Food consumption for each animal was determined weekly and mean daily diet consumption was calculated as g food/kg body weight/day. Compound intake (mg/kg/day) values were calculated as time-weighted averages from the consumption and body weight data.

4. Ophthalmoscopic examination

Eyes were not examined in this range-finding study.

5. Blood was collected from all animals from the jugular vein following overnight fasting prior to study initiation and at sacrifice 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)		
	(Thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

* Required for subchronic studies based on Subdivision F Guidelines

b. Clinical Chemistry

	ELECTROLYTES		OTHER
X	Calcium*	X	Albumin*
X	Chloride*	X	Blood creatinine*
	Magnesium	X	Blood urea nitrogen*
X	Phosphorus*	X	Total Cholesterol
X	Potassium*	X	Globulins
X	Sodium*	X	Glucose*
		X	Total bilirubin
	ENZYMES	X	Total serum protein (TP)*
X	Alkaline phosphatase (ALK)		Triglycerides
	Cholinesterase (ChE)		Serum protein electrophores
X	Creatine phosphokinase		
	Lactic acid dehydrogenase (LDH)		
X	Serum alanine amino-transferase (also SGPT)*		
X	Serum aspartate amino-transferase (also SGOT)*		
	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase		

* Required for subchronic studies based on Subdivision F Guidelines

6. Urinalysis*

Urine was not analyzed in this subchronic range-finding study.

* Not required for subchronic studies

7. Sacrifice and Pathology

All animals that died and those sacrificed on schedule were subjected to gross pathological examination and the CHECKED (X) tissues were collected for histological examination [E indicates that the organs were examined microscopically]. The (XX) organs, in addition, were weighed.

X	DIGESTIVE SYSTEM	X	CARDIOVASC./HEMAT.	X	NEUROLOGIC
	Tongue	X	Aorta*	XX	Brain*
X	Salivary glands*	XXE	Heart*	X	Periph. nerve*
X	Esophagus*	XE	Bone marrow*	X	Spinal cord (3 levels)[T]
X	Stomach*	XE	Lymph nodes*		
X	Duodenum*	XE	Spleen*	XXE	Pituitary*
X	Jejunum*	XE	Thymus*	X	Eyes (optic n.)[T]
X	Ileum*				
X	Cecum*		UROGENITAL		GLANDULAR
X	Colon*	XXE	Kidneys*+	XXE	Adrenal gland*
X	Rectum*	X	Urinary bladder*	XX	Lacrimal gland[T]
XXE	Liver*+	XXE	Testes*+	X	Mammary gland[T]
XX	Gall bladder*	XXE	Epididymides	XXE	Parathyroids*++
XE	Pancreas*	X	Prostate	XXE	Thyroids*++
			Seminal vesicle		
	RESPIRATORY	XXE	Ovaries		OTHER
X	Trachea*	X	Uterus*	X	Bone
XE	Lung*			X	Skeletal muscle
	Nose			X	Skin
	Pharynx			XE	All gross lesions and masses*
	Larynx				

* Required for subchronic studies based on Subdivision F Guidelines
+ Organ weight required in subchronic and chronic studies.
++ Organ weight required for non-rodent studies.
T = required only when toxicity or target organ

II. RESULTS

A. Observations :

1. Toxicity - No treatment-related toxicity or clinical signs were observed during the study. Clinical signs frequently observed in DMH-treatment groups (e.g., soft stool, diarrhea) were also observed in control animals.

2. Mortality - All animals survived until study termination.

B. Body weight and weight gain: There were no biologically significant differences in the mean weekly body weights or body weight gains of groups receiving diets containing DMH at any dos level compared with the means of appropriate control groups.

C. Food consumption and compound intake

1. Food consumption - There were no biologically significant differences in the mean grams of diet consumed per day for groups receiving DMH in the diet at any dosage level when compared to the means of the appropriate control groups. In general, groups receiving DMH consumed 5-24% more diet than did respective control groups. Only males in the nominal 120(ppm group exhibited decreased (90% control) diet consumption.

These changes in mean food consumption with respect to control values were not dose-related, may have represented random diet spillage by the test animals, and are therefore not considered to be treatment-related.

2. Compound consumption (time-weighted average):

Mean consumption of test compound (mg/kg/day) was calculated for each sex per group from the food consumption and body weight data. The results are presented in Table 1.

D. Ophthalmoscopic examination - No ophthalmological examinations were conducted during this dose range-finding study.

E. Blood work:

1. Hematology - As shown in the following Table 2, platelet counts at sacrifice in both males and females were quite variable, exhibiting values from 63-140% of control values. Although at 39600 ppm (HDT), this value was 63% of control in males and 67% of control in females, it is not possible to reach a firm conclusion that these decreases are treatment-related. Similar variability, which cannot be definitely related to treatment, was seen with respect to terminal leukocyte counts, particularly in males. Although the number of segmented neutrophils in males in the 39600 ppm group at sacrifice was 80% of control value and was decreased (80-96% control value) in all male groups, these decreases were not clearly dose-related, values were variable in females (81-117% controls, and these decreases are not considered to be related to treatment. Decreases (67-92% control value) were observed in the number of lymphocytes at sacrifice in females in all DMH-treatment groups. However, there was no clear dose-response, both increases and decreases (76-119% control value) were observed in males, and these differences with respect to controls are therefore not considered related to treatment with DMH for either sex.

Table 2. Hematology Values for Dogs Fed Diets Containing DMH for 8 Weeks[a]

Parameter	Males				
	0 ppm (Control)	1140 ppm (LDT)	3820 ppm (LMDT)	11550 ppm (HMDT)	39600 ppm (HDT)
Leukocytes $x10^3$/cmm					
Pretest	13.6± 1.70[b]	9.3± 2.47	6.9± 1.70	9.1± 2.83	10.2± 3.11
Terminal	8.7± 2.33	8.9± 0.92	7.6± 2.05	9.1± 0.35	6.6± 0.14

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Platelets x10^3/cmm					
Pretest	299±	308±	257±	383±	325±
	101.8	101.1	64.3	20.5	114.6
Terminal	338±	287±	277±	403±	213±
	43.1	86.3	3.5	28.3	25.5
Segmented Neutrophils x10^3/cmm					
Pretest	9.0±	6.1±	3.8±	6.1±	6.8±
	0.28	1.63	0.78	2.40	2.90
Terminal	4.9±	4.7±	4.3±	6.8±	3.9±
	2.05	0.49	1.56	2.90	0.35
	Females				
Leukocytes x10^3/cmm					
Pretest	11.9±	9.2±	7.9±	8.6±	9.9±
	1.41	1.84	0.78	0.85	4.03
Terminal	8.4±	8.6±	6.1±	8.2±	8.3±
	1.70	1.84	1.48	1.48	1.06
Platelets x10^3/ccm					
Pretest	310±	323±	279±	386±	329±
	72.8	4.2	38.2	27.6	140.7
Terminal	323±	297±	216±	450±	294±
	43.8	13.4	96.9	24.7	67.2
Lymphocytes x10^3/cmm					
Pretest	4.3±	3.1±	2.5±	3.0±	3.2±
	0.42	1.06	0.71	1.41	0.00
Terminal	3.9±	3.5±	2.6±	3.6±	3.3±
	0.49	0.57	0.78	0.92	0.07

[a]Data extracted from pages 43-50 of this submission (MRID No.: 43972101).
[b]Mean ± standard deviation from the mean.

2. Clinical Chemistry - There were no treatment-related changes in blood clinical chemistry values at any dose of DMH tested.

F. Urinalysis - Analyses of urine were not conducted in this range-finding study.

G. Sacrifice and Pathology:

1. Organ weight - There were no biologically significant differences from respective control values with regard to body weights, absolute organ weights, or organ/brain and organ/body weight ratios.

2. Gross pathology - No treatment-related findings were observed at gross necropsy.

3. Microscopic pathology -

a) Non-neoplastic - No treatment-related non-neoplastic lesions were observed during microscopic examination. Treatment-unrelated findings included: 1) mineralization of the renal medulla of the kidneys in all males and females (including controls); 2) interstitial pneumonia in lungs of 1 control male and 1 high-dose (39,600 ppm) female; 3) mild erythrophagocytosis of the mesenteric lymph node in 1 low-mid dose (3800 ppm) male; 4) mild parathyroid cyst in 2 high-mid dose (11,550 ppm) males, one control (0 ppm) female, and one low dose (1140 ppm) female; 5) giant cells in the testes of all males (including controls); 6) mild hemosiderosis in the heart of 1 control (0 ppm) female; 7) mineralization in the heart of 1 control (0 ppm) female and 1 high dose (39600 ppm) female; 8) mild lymphoid hyperplasia of the tracheobronchial lymph node in one low-mid dose (3800 ppm) female; and 9) mild colloid cyst of the thyroid in 1 low-mid dose (3820 ppm) female.

b) Neoplastic - No neoplastic lesions were observed in any control animals or test animals receiving DMH at any dose level tested.

III. **DISCUSSION**

A. This dose range-finding study (MRID No.: 43972100) for the previously submitted and reviewed one-year dog chronic toxicity study (MRID No.: 43553101) was used to set the nominal dose levels at 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) in the definitive study (MRID No.: 43553101). Only a summary of this dose range-findin study (MRID No. 43972100) was included with the previously reviewed definitive study (MRID No.: 43553101). The data presented in this dose range-finding study indicate that 5,5-dimethylhydantoin elicited no significant effects on any parameter examined in male or female purebred beagle dogs at doses up to 39600 ppm (HDT) in the diet (corresponding to 1598 mg/kg/day in males and 1650 mg/kg/day in females). Therefore, **the LEL > 39600 ppm (HDT) in the diet, based on the lack of any observed adverse effects. The NOEL ≥ 39600 ppm (HDT) in the diet.**

B. Study deficiencies: This study contains no significant deficiencies.