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

OCT 7 1987

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Review of a one-year chronic dog study with Cyanazine and amendment to the final report.
EPA ID # 352-475, EPA Accession #'s 400819-01 and 402290-01; Caswell #188C; Tox Branch Project No.'s 7-0832 and 7-0873.

TO: Robert J. Taylor/Yowell (PM-25)
Herbicide-Fungicide Branch
Registration Division (TS-767)

FROM: Stephen C. Dapson, Ph.D. Stephen C. Dapson 10/5/87
Pharmacologist, Review Section V
Toxicology Branch/HED (TS-769C)

THRU: Quang Q. Bui, Ph.D., D.A.B.T. Quang Q. Bui 10/5/87
Acting Section Head, Review Section V
and
Theodore M. Farber, Ph.D., D.A.B.T.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Registrant: E. I. duPont de Nemours & Co. (Inc.)
Agricultural Products Department
Walker's Mill Building
Barley Mill Plaza
Wilmington, Delaware 19898

Action Requested: Review a one-year chronic dog study and an attachment to the one-year dog study, with Cyanazine.

Recommendations: The one-year dog study with Cyanzine is acceptable and is classified as Core-Minimum Data.

The No Observed Effect Level (NOEL) for systemic toxicity is 25 ppm (both sexes). The Lowest Observed Effect Level (LOEL) for systemic toxicity is 100 ppm based on reduced body weights and body weight gains, elevated platelet counts, reduced levels of total protein, albumin and calcium in males and females. There were also slight, not statistically significant, decreases in spleen weights and increases in liver weights in the females and increases in liver weights and decreases in testes weights in the males. No gross or microscopic findings related to treatment were noted.

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Primary Reviewer: Stephen C. Dapson, Ph.D
Review Section V, Tox. Branch/HED (TS-769C)

Secondary Reviewer: Quang Q. Bui, Ph.D., D.A.B.T.
Acting Section Head, Review Section V, Tox. Branch/HED (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: Chronic Toxicity - Non Rodent (Dog)
Guideline: §83-1

EPA IDENTIFICATION NUMBERS: EPA ID No. 352-475
EPA Record No.'s 199269 & 198645
EPA Accession No.'s 40081901 & 40229001
Shaughnessy No. 100101
Caswell No. 188C
Tox. Branch Project No's 7-0832 & 7-0873
MRID No.'s 40081901 & 40229001

TEST MATERIAL: Cyanazine
2-[(4-chloro-6-[ethylamino]-s-triazin-2-yl)amino]-
2-methyl propionitrile

SYNONYMS: Bladex®, Technical Grade, SD 15418, ID # WRC 107F

STUDY NUMBER(S): HLA Study No. (DuPont Report No.) 6160-104
Shell Protocol No. WTP 277

Addendum to above:
Laboratory Project ID (DuPont Report No.) WRC-RIR-480
Protocol No. WTP-277
Project No. 80276 (T 84-567)

SPONSOR: E. I. duPont de Nemours & Co. (Inc.)
Agricultural Products Department
Walker's Mill Building
Barley Mill Plaza
Wilmington, Delaware 19898

TESTING FACILITY: Hazelton Laboratories America, Inc.
3301 Kinsman Boulevard
Madison, Wisconsin 53704

Addendum to Study:
Shell Oil Company
Westhollow Research Center
3333 Highway 6 South
Houston, Texas

TITLE OF REPORT: One-Year Oral Dosing Study in Dogs with the
Triazine Herbicide-Cyanazine

Addendum to above:
Analysis of Technical Bladex, WRC Tox Sample
No. 107F in Dog Chow

AUTHOR Bruce C. Dickie
addendum author J. R. Dawson

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REPORT ISSUED December 30, 1986
addendum date: February 18, 1987

CONCLUSIONS

The No Observed Effect Level (NOEL) for systemic toxicity is 25 ppm. The Lowest Observed Effect Level (LOEL) for systemic toxicity is 100 ppm based on reduced body weights and body weight gains, elevated platelet counts, reduced levels of total protein, albumin and calcium in males and females. There were also slight, not statistically significant, decreases in spleen weights and increases in liver weights in the females and increases in liver weights and decreases in testes weights in the males. No gross or microscopic findings related to treatment were noted.

Classification: Core-Minimum Data.

Special Review Criteria (40 CFR 154.7)

NONE

A. MATERIALS: A copy of the "materials and methods" section from the investigator's report is appended.

1. Test compound: Cyanazine (technical Bladex); Description: white crystalline solid; Batch #06-AMK-5406; Purity 98%; contaminants: not provided.

2. Test animals: Species: Dog; Strain: Beagle; Age: 5 months; Weight: 5.4-8.8 kg at study initiation; Source: Marshall Research Animals (North Rose, New York).

Animals were acclimated for "approximately 3 weeks" with daily examinations for clinical abnormalities. The animals also received "a complete physical examination, two fecal flotations for parasites, and weekly measurement of body weight". The animals were "screened" for ecto- and endoparasites. Several animals had evidence of coccidiosis and were eliminated from the study prior to selection of study groups. The animals were kept under standard animal care conditions (see attached "materials and methods").

B. STUDY DESIGN:

1. Animal assignment

Seventy animals were received, 60 animals were arranged by weight and assigned randomly to the following test groups:

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Test Group	Dose in diet (ppm)	Main Study 12 months male	female
1 Cont.	0	6	6
2 Low (LDT)	10	6	6
3 Low Mid (LMDT)	25	6	6
4 High Mid (HMDT)	100	6	6
5 High (HDT)	200	6	6

No interim sacrifice scheduled.

2. Diet preparation

Diet was prepared every 4-6 weeks and stored at ambient temperature, initially, then after "MIX 3", the finished diets were stored refrigerated. Samples of treated food were analyzed for stability and concentration for all "MIXES". Diet preparation procedure is presented in the attached "materials and methods" copy.

Results - Diet was considered "stable at refrigerator temperature (about 5°C) for at least 8 weeks" (tested only on "MIX" #1). Samples of all mixes were analyzed for concentration with no variations greater than ± 10%. Homogeneity testing was conducted on "MIXES" #1, 5, 8 and 12 (of the 12 total mixings). Again, no variations were greater than ± 10%.

3. Animals received food (Certified Canine Diet® #5007, Ralston Purina Company) and tap water ad libitum. The diet was analyzed by the manufacturers. The water was analyzed by HLA for total dissolved solids, conductivity, microbiological content, selected elements, heavy metals, organophosphates and chlorinated hydrocarbons. Coliform screens were conducted.

4. Statistics - The following procedures were utilized in analyzing the numerical data:

One-way analysis of variance (ANOVA) on raw or transformed data
Analysis of covariance (ANCOVA)
One-tailed Dunnett's t-test
Two-tailed Dunnett's t-test

A signed Statement of "No Data Confidentiality Claims" was included.

A signed statement of compliance with EPA/OPP GLP's was included.

A signed "Quality Assurance Statement" was included.

A listing of Key Personnel involved in the study was included.

Copies of the protocol and deviations from the protocol were included.

C. METHODS AND RESULTS:

1. Observations

Animals were inspected twice daily for signs of toxicity, mortality and "general physical appearance."

Toxicity/Mortality (survival)

No deaths were reported. The investigators only provided individual animal data for clinical observations. They stated that "There were no treatment-related observations." However, inspection of data from control and high dose males indicates that there may be dose-related differences in certain observations. For example, the high dose males had approximately twice the number of animal days (total number of days with a particular observation divided by the number of animals in a particular group) with evidence of soft stool as compared to the control group.

2. Body weight

Animals were weighed and recorded weekly during "acclimation", at study initiation, weekly throughout study and at time of sacrifice. The following Table I presents body weight gain at selected intervals and Graphs 1 and 2 (appended from the investigator's report) presents the mean body weights of the males and females, respectively, for the entire treatment period.

As can be noted in the data provided, There was a decrease in body weight (statistically significant) and body weight gain in both males and females of the 100 and 200 ppm group throughout the entire study.

3. Food consumption and compound intake

Food consumption was determined and mean daily diet consumption was calculated. Compound intake was calculated from the food consumption data. Food efficiency was not calculated by the investigators.

Table I: Body Weights and Body Weight Gains at Selected intervals (kg)[a] 006350

	Males					Females				
Dose(ppm):	Cont.	10	25	100	200	Cont.	10	25	100	200
Week										
0	7.3	7.2	7.6	7.4	7.6	6.4	6.5	6.4	6.4	6.4
1	7.4 (0.1)†	7.2 (0)	7.6 (0)	7.1* (-0.3)	7.0* (-0.6)	6.5 (0.1)	6.6 (0.1)	6.5 (0.1)	6.2* (-0.2)	5.9* (-0.5)
4	8.2 (0.9)	8.0 (0.8)	8.4 (0.8)	7.5* (0.1)	7.3* (-0.3)	7.3 (0.9)	7.2 (0.7)	7.3 (0.9)	6.5* (0.1)	6.2* (-0.2)
7	9.1 (1.8)	8.8 (1.6)	9.2 (1.6)	8.0* (0.6)	7.9* (0.3)	8.1 (1.7)	8.0 (1.5)	8.0 (1.6)	7.0* (0.6)	6.7* (0.3)
10	9.7 (2.4)	9.4 (2.2)	9.7 (2.1)	8.2* (0.8)	8.2* (0.6)	8.5 (2.1)	8.3 (1.8)	8.4 (2.0)	7.1* (0.7)	6.7* (0.3)
16	10.4 (3.1)	10.3 (3.1)	10.3 (2.7)	8.6* (1.2)	8.7* (1.1)	9.0 (2.6)	8.9 (2.4)	9.0 (2.6)	7.4* (1.0)	7.0* (0.6)
22	10.9 (3.6)	10.9 (3.7)	11.0 (3.4)	9.2* (1.8)	9.3* (1.7)	9.7 (3.3)	9.3 (2.8)	10.0 (3.6)	7.8* (1.4)	7.4* (1.0)
28	11.0 (3.7)	11.0 (3.8)	11.2 (3.6)	9.1* (1.7)	9.4* (1.8)	9.8 (3.4)	9.4 (2.9)	10.0 (3.6)	7.6* (1.2)	7.4* (1.0)
34	11.0 (3.8)	11.2 (4.0)	11.6 (4.0)	9.6* (2.2)	9.6* (2.0)	10.1 (3.7)	9.6 (3.1)	10.2 (3.8)	7.9* (1.5)	7.7* (1.3)
40	11.3 (4.0)	11.7 (4.5)	11.9 (4.3)	9.8* (2.4)	9.8* (2.2)	10.5 (4.1)	9.9 (3.4)	10.5 (4.1)	8.1* (1.7)	7.9* (1.5)
46	11.4 (4.1)	11.9 (4.7)	11.9 (4.3)	9.9* (2.5)	9.9* (2.3)	10.8 (4.4)	9.8 (3.3)	10.8 (4.4)	8.2* (1.8)	8.1* (1.7)
52	11.4 (4.1)	12.0 (4.8)	11.8 (4.2)	10.0* (2.6)	10.0* (2.4)	10.7 (4.3)	9.9 (3.4)	11.0 (4.6)	8.0* (1.6)	7.9* (1.5)

* = $p < 0.05$

† = body weight gains calculated by reviewer, from body weight at specific week minus body weight at week 0;

[a] - Data extracted from HLA Study No. 6160-104, Table 5.

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Cyanazine

RIN 3332-96

Page_____ is not included in this copy.

Pages 7 through 8 are not included.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

✓ FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Food consumption/Food Efficiency/Compound Intake

No biologically relevant differences were noted in food consumption. Food efficiency calculated by this reviewer also showed no biologically relevant differences. Compound intake calculated by the investigators is presented on the following table:

Summary of Calculated Compound Consumptions[a]
(mg/kg body weight/day)

	Cyanazine (ppm)							
	Males				Females			
	10	25	100	200	10	25	100	200
Mean	0.27	0.68	3.20	6.11	0.28	0.72	3.02	6.39
s.d.(±)	0.038	0.094	0.342	0.646	0.047	0.126	0.373	0.820

Formula to calculate compound consumptions:
Mean daily food consumption (g) x $\frac{\text{Dose level (ppm)}}{1{,}000}$ ÷ Mean body weight (kg)

[a] = Data extracted from HLA Study No. 6160-104, Table 9.

4. Ophthalmalogical examinations

Examinations were performed prior to study initiation for base-line values and at study termination on all animals. No remarkable observations were noted in the individual animal data presented.

5. Blood was collected before study initiation and at 13, 26, 38 and 72 weeks for hematology and clinical analysis from all animals. Animals were fasted overnight. The CHECKED (X) parameters were examined.

a. Hematology

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 (Thromboplastin time) (Clotting time) (Prothrombin time)	X	Nucleated red blood cells

* Required for subchronic and chronic studies

The investigators supplied both mean and individual animal data. Platelet counts were occasionally higher in both males and females of the 100 and 200 ppm groups, although no values were statistically significant. No biologically relevant differences were noted in other hematological parameters. Blood clotting measurements were not taken.

b. Clinical Chemistry

X	Electrolytes:	X	Other:
X	Calcium*	X	Albumin*
X	Chloride*	X	Blood creatinine*
	Magnesium*	X	Blood urea nitrogen*
X	Phosphorous* (inorganic)	X	Cholesterol* (total)
X	Potassium*	X	Globulins
X	Sodium*	X	Glucose*
	Enzymes	X	Total Bilirubin*
X	Alkaline phosphatase	X	Total Serum Protein*
	Cholinesterase#		Triglycerides
X	Creatinine phosphokinase*°		Serum protein electrophoresis
X	Lactic acid dehydrogenase	X	Diet Bilirubin
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

Decreased levels of total protein, albumin and calcium were consistently noted on weeks 13, 26, 38, and 52 in both males and females of 200 ppm study group. The 100 ppm group occasionally presented with decreased levels of the same parameters (especially males at week 52). Inorganic phosphorus was noted to occasionally increase, probably linked with the decreases in calcium levels. Other measured parameters showed no biologically relevant differences.

6. Urinalysis°

Urine was collected from fasted animals at weeks 13, 26, 38 and 52. The CHECKED (X) parameters were examined.

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

* Required for chronic studies
° Not required for subchronic studies

No treatment related findings were noted.

7. Sacrifice and Pathology -

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

X	Digestive system
	Tongue
X	.Salivary glands*
X	.Esophagus*
X	.Stomach*
X	.Duodenum*
X	.Jejunum*
X	.Ileum*
X	.Cecum*
X	.Colon*
X	.Rectum*
X	.Liver*†
XX	Gall bladder*#
X	.Pancreas*
	Respiratory
X	.Trachea*
XX	.Lung*
	Nose°
	Pharynx°
	Larynx°

X	Cardiovasc./Hemat.
X	.Aorta*
XX	.Heart*
X	.Bone marrow*
X	.Lymph nodes*
XX	.Spleen*
X	.Thymus*
	Urogenital
XX	.Kidneys*†
X	.Urinary bladder*
XX	.Testes*†
X	Epididymides
X	Prostate
X	Seminal vesicle
XX	Ovaries*†
X	.Uterus*
X	Cervix
X	Oviducts

X	Neurologic
XX	.Brain*†
X	Periph. nerve*#
X	Spinal cord (3 levels)*#
X	.Pituitary*
X	Eyes (optic n.)*#
	Glandular
XX	.Adrenals*
	Lacrimal gland#
X	Mammary gland*#
XX	.Parathyroids*††
XX	.Thyroids*††
	Other
X	Bone*#
X	Skeletal muscle*#
X	Skin*#
X	All gross lesions and masses*

* 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. Organ weight

The investigators provided summary and individual animal data for absolute organ weights, relative organ weights, and organ to brain weight ratios. The following Table (II) presents selected organ weight comparisons. The relative heart weights of the females of the high dose were statistically significant from control, however, the absolute organ weight and organ to brain weight ratios do not support this. A similar situation exists for lung and kidney (2) weights of females in the 100 and 200 ppm dose groups. The spleen weights of females in the 100 and 200 ppm dose groups, although not statistically significantly different, do show a slight, dose related, reduction. The liver weights of both males and females of the 100 and 200 ppm dose groups show a slight increase over control (not statistically significant). The testes weight of the high dose males were reduced when compared to that of the control (not statistically significant). The adrenal glands of the high dose animals showed a statistically significant decrease in relative weight, however, this was not supported by absolute organ weight or organ to brain weight ratios.

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Table II: Organ Weight Data[a]

Dose(ppm)		Heart	Lung	Spleen	Kidneys	Liver	Gonads
		Males					
Control	A†	93.20	80.16	30.77	24.55	25[illegible]	8.477
	R††	.8487	.7350	.2834	.2281	2.3352	.0778
	O/B†††	1.1911	1.0202	.3931	.3123	3.2301	.1060
10	A	89.77	72.16	35.65	25.29	283.12	8.907
	R	.7822	.6270	.3110	.2197	2.4508	.0773
	O/B	1.0454	.8369	.4114	.2935	3.3033	.1035
25	A	93.31	83.83	33.00	24.75	266.54	8.794
	R	.8300	.7421	.2921	.2176	2.3510	.0782
	O/B	1.1476	1.0289	.4023	.3033	3.2578	.1080
100	A	86.28	81.67	25.60	24.19	245.48	7.242
	R	.9248	.8810*	.2676	.2636	2.5625	.0800
	O/B	1.0948	1.0385	.3241	.3068	3.1077	.0918
200	A	83.25	72.77	26.82	25.78	267.22	6.034
	R	.8744	.7715	.2871	.2714	2.7908*	.0651
	O/B	1.0101	.8839	.3259	.3144	3.2319	.0749
		Females					
Control	A	70.32	65.13	34.47	18.38	247.46	.554
	R	.6940	.6431	.3559	.1805	2.4383	.0057
	O/B	.8832	.8196	.4638	.2313	3.1097	.0070
10	A	74.13	64.53	34.35	18.61	242.82	.761
	R	.7813	.6831	.3651	.1958	2.5649	.0079
	O/B	.9350	.8148	.4344	.2351	3.0693	.0096
25	A	82.43	65.70	45.27	19.92	284.33	.634
	R	.7783	.6236	.4158	.1872	2.6679	0060
	O/B	1.0234	.8163	.5582	.2475	3.5338	.0079
100	A	65.31	58.93	26.56	16.37	207.67	.444
	R	.8478	.7667*	.3445	.2127*	2.7032	.0058
	O/R	.9047	.8194	.3745	.2268	2.8907	.0061
200	A	68.30	61.70	24.85	16.94	204.95	.438
	R	.9035*	.8225*	.3309	.2246*	2.7295	.0060
	O/R	.9355	.8449	.3410	.2322	2.8065	.0060

* = $p < 0.05$

† = A = Absolute Organ Weight (gm)

†† = R = Relative Organ Weight (organ to body weight percentages)

††† = O/B = Organ to Brain Weight Ratios

[a] = Data extracted from HLA Study No. 6160-104, Tables 17, 18 and Appendix D.

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b. Gross pathology

The investigators provided group summary and individual animal data. Observations consisted of one male in the 10 ppm group, and two females, one each in the control and 10 ppm group with light focus areas of the lungs and one male in the 25 ppm group with a raised focus area of the lung. Two males, one each in the control and 25 ppm group had light focus areas of the liver. One male in the 200 ppm group had spleen adhesions and two males, one each in the control and 10 ppm group had raised focus areas of the spleen. One male and one female in the 100 ppm group had red focus areas of the ileum and one female of the 25 ppm group had a diffusely red ileum. Three males, one each in the 10, 25 and 100 ppm groups had red focus areas of the colon. One male in the 200 ppm group had a red focus area of the skin and two males, one each in control and the 25 ppm group along with one female in the 200 ppm group showed alopecia. One male had a large cervical lymph node. Two males of the 200 ppm group and one control female had a diffusely red mesenteric lymph node and one 200 ppm female had a mottled mesenteric lymph node. One control male had a thickened wall of the urinary bladder. One 10 ppm male had a light focus area of the epididymides. One 10 ppm female had a cyst on the uterus. One 25 ppm male and one 100 ppm female had a diffusely red pinna. None of these observations appear to be related to treatment.

c. Microscopic pathology

1) Non-neoplastic

The investigators provided group summary and individual animal data. Table III presents the summary of the findings.

No apparent treatment related findings were noted in the data provided.

Table III: Summary of Microscopic Observations

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Dose (ppm):	Control	10	25	100	200
#males/#females examined	6/6	6/6	6/6	6/6	6/6
Lung:					
Alveolar Macrophages	1/0†	1/0	0/0	0/0	0/0
Fibrosis	1/1	1/2	0/0	0/0	0/0
Hemorrhage	1/0	0/0	1/0	0/0	0/0
Inflammation	1/1	2/1	2/3	0/0	2/0
Kidneys:					
Hyaline Casts	1/0	1/0	0/0	0/1	1/0
Mineralization (pelvis)	3/4	1/3	1/2	3/4	3/2
Pigment	1/0	0/0	1/0	0/0	0/0
Pyelonephritis	1/0	0/0	1/0	0/0	1/0
Heart:					
Inflammation	1/0	0/0	0/1	0/0	0/0
Liver:					
Fibrosis (capsule)	1/0	0/0	0/0	0/0	0/0
MCI††	5/1	2/0	3/0	0/0	2/2
Vacuolation	1/0	0/0	1/0	0/0	0/0
Spleen:					
Cyst (capsule)	1/0	1/0	0/0	0/0	0/0
Fibrosis (capsule)	1/0	0/0	0/0	0/0	1/0
Hemorrhage (artery)	1/1	0/1	1/0	1/2	1/0
Hemorrhage (capsule)	1/0	3/0	0/0	1/0	0/0
Mineralization (artery)	1/1	0/2	1/0	1/2	2/0
Mineralization (capsule)	1/0	3/0	0/1	1/0	0/0
Pigment (artery)	1/1	0/2	1/0	1/2	2/0
Pigment (capsule	1/0	3/0	0/0	0/0	0/0
Thyroid(s):					
Inflamation	1/0	1/0	0/0	0/0	0/0
Ultimobranchial Cysts	1/2	0/1	1/0	1/1	1/2
Parathyroid(s):					
Cysts	1/0	0/0	1/2	2/0	0/1
Pituitary:					
Cyst	3/4	2/1	0/2	2/5	1/2
Ileum:					
Congestion	1/0	0/0	0/1	0/0	0/0
Colon:					
Congestion	1/0	0/0	0/0	1/0	0/0
Skin:					
Erosion/Ulceration	1/0	0/0	0/0	0/0	0/1
Inflammation	1/0	0/1	1/0	0/1	1/0
Cervical Lymph Node:					
Pigment	1/0	1/0	0/0	0/0	0/2
Mesenteric Lymph Nodes:					
Congestion:	1/1	0/0	0/0	2/0	2/0
Thymus:					
Cysts	1/0	3/1	1/0	2/0	0/0
Uterus:					
Diluted lumen	0	0	1	0	0
Pinna:					
Inflammation	1/0	0/0	0/0	0/1	0/0

† = #male observations/#female observations

†† = MCI = mononuclear cell infiltration

a = Data extracted from HLA Study No. 6160-104, Table 20 and Appendix D.

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2) Neoplastic

No neoplastic observations were noted

D. DISCUSSION:

The major treatment related findings in this study were reduced body weights and body weight gains in the 100 and 200 ppm males and females. Further, platelet counts were higher in both males and females of the 100 and 200 ppm dose groups along with decreased levels of total protein, albumin and calcium. Inorganic phosphorus levels were seen to increase occasionally (possibly due to decreased calcium levels). No other hematology, clinical chemistry or urinalysis parameters were affected. There were slight, not statistically significant decreases in spleen weights and increases in liver weights (both absolute and relative organ weights) over control in the females of the 100 and 200 ppm dose group. Males of the 100 and 200 ppm dose groups had slight increases in liver weights and decreases in testes weight in the 200 ppm group (absolute and relative organ weights). Gross and microscopic pathology showed no treatment related findings. The No Observed Effect Level (NOEL) for systemic toxicity is 25 ppm with the Lowest Observed Effect Level (LOEL) for systemic toxicity of 100 ppm.

Cyanazine

RIN 3332-96

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