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E. I. du Pont de Nemours and Co., Inc.
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HASKELL LABORATORY REPORT NO. 326-82 MR NO. [redacted]

Material Tested: [redacted]

Haskell No.: 14,008

Other Codes: [redacted]

Study Initiated/Completed: 5/4/81 - 5/29/81

Material Submitted by: [redacted]
Polymer Products Department
Experimental Station

TEN-DOSE ORAL SUBACUTE TEST IN RATS [redacted]

Summary: [redacted] was administered orally to young adult Crl:CD® male rats at repeated dose levels of either 1,000 mg/kg, 100 mg/kg or 10 mg/kg for 10 days over a 2-week period. Clinical signs observed included: weakness, stained perineal area, lethargy, prostration, humped-posture, congestion, chromodacryorrhea and weight loss. Compound-induced macroscopic and microscopic lesions were present in the thymus, spleen, bone marrow and kidneys of high-dose animals. Because of the mortality seen in the high-dose group, reversibility of these lesions could not be adequately evaluated. No treatment-related lesions were observed in the low or intermediate dose groups.

Statistical analysis of clinical laboratory measurements data showed that rats dosed 10 times with [redacted] at levels of 100 mg/kg and 1,000 mg/kg had higher than normal erythrocyte counts and hematocrits which appeared to be related to the dose. Rats dosed with 1,000 mg/kg [redacted] had higher leukocyte counts, almost twice the normal range established by the controls. These animals also showed a three-fold increase in serum blood urea nitrogen and increased hemoglobin, serum glutamic pyruvic transaminase activity, and creatinine. The 100 mg/kg treated rats showed a slight increase in serum total protein. An increase in

the relative number of neutrophils (1,000 mg/kg group) and a slight to moderate hypochromia (100 mg/kg and 1,000 mg/kg groups) was seen.

In the recovery groups, a slight increase in serum creatinine levels in the 100 mg/kg treated rats was observed. In the absence of this parameter being significantly different prior to the recovery period, the significance of the finding is questionable. No other differences were detected in the clinical pathologic parameter studies in the recovery rats (only 1 rat was examined in the 1,000 mg/kg group).

Analysis of blood for organofluoride revealed a dose-related increase in concentration following the 10th dose (1, 30, 79, and 197 ppm, exposures of 0, 10, 100, and 1,000 mg/kg, respectively). These values dropped to 0.5, 12, 25, and 25 ppm (1 rat), 0 to 1,000 mg/kg, respectively, 14 days after the last treatment, indicating clearance from the blood is relatively slow.

Procedure: The test material, as an aqueous solution at concentrations of either 10%, 1% or 0.1%, was administered by intragastric intubation to 3 groups of young adult Crl:CD® male rats, 10 rats per group, 5 times a week for 2 weeks at repeated dose levels of either 1,000 mg/kg, 100 mg/kg or 10 mg/kg; an additional group of 10 rats served as controls and was intubated with distilled water. Two test rats at 1,000 mg/kg died before the 6th dose and 1 before the 9th dose. Five control and 14 test rats were sacrificed approximately 4 hours after the last dose. Two test rats at 1,000 mg/kg died during the recovery period. The remaining 5 controls and 11 test rats were observed over a 14-day recovery period and then sacrificed. All rats were examined grossly, selected tissues were weighed and selected tissue and organs were evaluated histologically. Clinical pathology measurements were taken on all surviving rats 4 hours after the 10th dose and after the 14-day recovery period. Blood was also collected at the same periods for fluorine analysis.

Results:

Dose (mg/kg/day)	No. of Doses	Mort 'ty	Clinical Signs
1.000	10	9/10	First Week: Weakness and weight loss. Second Week: Weakness, stained perineal area, lethargy, prostration, humped posture and weight loss. Two rats died before the 6th dose and 1 died before the 9th dose. Recovery Period: Weakness, congestion humped posture, chromodacryorrhea and weight loss. Two rats died during the recovery period.
100	10	0/10	First Week: Slight weight loss. Second Week: Slight weight loss. Recovery Period: None.
10	10	0/10	First Week: Slight weight loss. Second Week: Slight weight loss. Recovery Period: None.

Pathologic Changes: See Appendix A (Pathology Report No. [redacted].)

Clinical Pathology: See Appendix B (Clinical Report for [redacted] 6/29/81).

Fluorine Analysis: See Appendix C (Analytical Report Job No. [redacted]).

Synonym: [redacted]

Composition: [redacted]

Purity: [redacted]

Contaminants: [redacted]

Report by: John A. Hall
John A. Hall
Technician

Reviewed by: O. Louis Dashiell
O. Louis Dashiell
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JAH:jrg:WP:1.22
Date Issued: June 3, 1982
[redacted]
Report No. 326-82

ES-3442

APPENDIX A

E. I. DU PONT DE NEMOURS & COMPANY
INCORPORATED
HASKELL LABORATORY FOR TOXICOLOGY
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ELKTON ROAD, NEWARK, DELAWARE 19711

CENTRAL RESEARCH AND DEVELOPMENT DEPARTMENT

Pathology Report No. [redacted]

[redacted]

H-14008 [redacted]

Polymer Products Department & Chemical & Pigments Department

Oral Subacute Study in CD® Rats

April 21, 1982

Summary

Compound-induced macroscopic and microscopic lesions were present in the thymus (Lymphocytic depletion), spleen (Lymphocytic depletion), bone marrow (Hypocellularity), and kidneys (Nephritis) of high-dose animals. Because of excessive mortality in the high-dose group, reversibility of these lesions was not adequately evaluated. Compound-induced lesions were not observed in the low or intermediate-dose groups.

Introduction

Every animal (except #301558) in this study was given a complete post-mortem examination. Microscopic examinations were also performed on selected tissues from each available animal.* Groups I (0 mg/kg), II (1000 mg/kg), III (100 mg/kg), and IV (10 mg/kg) consisted of ten male rats each. Each group had a 12 day feeding phase and a 14 day recovery phase except the

* Adrenal Glands, Thyroid Gland, Parathyroid Glands, Esophagus, Stomach, Duodenum, Ileum, Jejunum, Cecum, Colon, Liver, Spleen, Bone Marrow, Thymus, Heart, Sternum, Eyes, Brain, Trachea, Lungs, Kidneys, Testes and Epididymides.

high-dose group. Due to marked clinical toxicity and early mortality in this group, only one rat survived the 14 day recovery period. Two additional high-dose rats survived for three and seven days in the recovery phase.

Histomorphological lesions were tabulated by individual animal in Table I and were summariz d in Table II.

Results

Macroscopically, compound-induced tissue alterations were restricted to the spleen (splenic atrophy - 3 rats) and thymus (thymic atrophy - 3 rats) in the high-dose group. Both lesions were associated microscopically with mild to severe lymphocytic depletion. Animals from all groups had multifocal areas of reddish-gray mottling in the pulmonary parenchyma. These lesions were associated histomorphologically with multifocal areas of granulomatous interstitial pneumonitis.

Microscopically, compound-induced lesions were present in the spleen (lymphocytic depletion - 7 of 9), bone marrow (hypocellularity - 5 of 7), thymus (lymphocytic depletion - 5 of 8), and kidneys (purulent tubulointerstitial nephritis - 8 of 9), of the high-dose group. Compound-induced lesions were not present in the other test groups.

The renal lesion in this study was rather unique in that there was selective toxicity for the distal and collecting tubules and the medulla was more severely affected than the cortex. The lesion was characterized by degeneration and regeneration of the tubular epithelium with tubular ectasia. This was associated with a marked interstitial infiltration with neutrophils and edema fluid. Occasionally, there were small foci of renal papillary necrosis associated with the neutrophilic exudate. One rat (#301555

- Group II) that survived the 14-day recovery period did not have similar compound-induced lesions.

There were several other microscopic inflammatory and/or degenerative lesions that were considered, because of their common occurrence and/or their low frequency, to be incidental spontaneous lesions in this group of rats.

Report by: William D. Kerns, D.V.M.
Senior Research Pathologist

Approved by: William C. Knauss, D.V.M.
Manager, Pathology Division

WDK:WCK:wfd

PATHOLOGY TABLE CODES

* Tissue Accounting Code:

L = Lesion observed

N = No significant lesion observed

O = Tissue missing

I = Tissue insufficient for histomorphologic evaluation

N = Only one gland is present and it is normal

Q = Specimen quality is inadequate for an accurate assessment of subtle tissue alteration, otherwise the tissue appears to be normal

A = Autolysis

P = Present

** Degree of Change:

1 = Minimal

2 = Mild

3 = Moderate

4 = Marked

5 = Severe

*** Mode of Death:

S = Sacrificed

D = Unscheduled death

TABLE I

INDIVIDUAL ANIMAL HISTOPATHOLOGY DATA

Tissue*/ Observations**	Group:	I										II									
	Dose:	0 mg/kg										1000 mg/kg									
	Mode of Death:	S	S	S	S	S	S	S	S	S	S	S	S	D	S	S	S	D	D	D	D
	Sex:	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
	Days on Test:	12	12	12	12	12	26	26	26	26	26	12	12	10	12	12	26	8	15	19	8
	Recovery Days:	0	0	0	0	0	14	14	14	14	14	0	0	0	0	0	14	0	3	7	0
	Rat No. 301-:	544	543	542	541	540	545	546	547	548	549	550	551	552	553	554	555	556	557	558	559
ENDOCRINE SYSTEM																					
Adrenal Gland (a)		N	N	I	N	N	N	N	I	N	N	N	N	N	N	N	N	N	A	O	N
Thyroid Gland		N	N	I	N	I	N	N	O	O	N	I	N	N	N	N	O	N	O	O	O
Parathyroid Gland (a)		O	O	O	O	N	N	O	O	O	O	O	O	N	N	N	O	O	O	O	O
GASTRO INTESTINAL SYSTEM																					
Esophagus		N	N	I	N	N	N	N	N	N	N	N	N	N	L	N	N	N	A	O	N
Periesophagitis, granulomatous, focal		-	-	-	-	-	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-
Stomach		N	N	N	N	N	N	N	N	N	N	N	N	L	N	N	N	N	O	O	A
Glandular, atrophy, diffuse		-	-	-	-	-	-	-	-	-	-	-	-	3	-	-	-	-	-	-	-
Duodenum		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	O	O	A
Ileum		N	N	N	N	N	N	N	N	N	N	.	N	A	N	N	N	A	O	O	A
Jejunum		N	N	N	N	O	N	N	N	N	N	N	N	A	N	N	N	A	O	O	A
Cecum		N	N	N	N	N	N	P	O	N	N	N	N	A	N	N	N	A	O	O	A
Colon		N	N	N	N	N	N	N	X	N	N	N	N	A	N	N	N	N	O	O	A
Liver		Q	N	Q	N	Q	Q	Q	N	Q	Q	Q	Q	N	N	Q	Q	N	A	O	N

TABLE I (Continued)

INDIVIDUAL ANIMAL HISTOPATHOLOGY DATA

Part 2

Tissue*/ Observation**	Group:	I										II									
	Dose:	0 mg/kg										1000 mg/kg									
	Mode of Death:	S	S	S	S	S	S	S	S	S	S	S	S	D	S	S	S	D	D	D	D
	Sex:	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
	Days on Test:	12	12	12	12	12	26	26	26	26	26	12	12	10	12	12	26	8	15	19	8
	Recovery Days:	0	0	0	0	0	14	14	14	14	14	0	0	0	0	0	14	0	3	7	0
	Rat No. 301-:	544	543	542	541	540	545	546	547	548	549	550	551	552	553	554	555	556	557	558	559
Hepatitis, necrotic, purulogranulomatous, multifocal		-	-	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-	-	-	-
Hepatitis, lymphocytic, focal		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HEMOPOIETIC SYSTEM																					
Spleen		N	N	N	N	N	N	N	N	N	N	L	L	L	L	N	N	L	L	0	L
Lymphocytic depletion, diffuse		-	-	-	-	-	-	-	-	-	-	2	2	4	1	-	-	5	3	-	5
Bone Marrow		N	N	N	I	N	I	N	N	N	N	I	L	L	L	L	N	N	A	0	L
Hypocellularity, diffuse		-	-	-	-	-	-	-	-	-	-	-	2	2	2	1	-	-	-	-	2
Thymus		N	N	N	N	N	N	N	N	N	N	L	L	0	N	N	L	L	L	0	L
Lymphocytic depletion, diffuse		-	-	-	-	-	-	-	-	-	-	3	3	-	-	-	-	5	5	-	5
Thymusitis, pyogranulomatous, focal		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	-	-	-	-
Thymic Lymph Node		N	N	0	N	N	N	N	N	N	N	N	N	0	N	N	N	N	0	0	N
Lymphocytic hyperplasia, diffuse		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
MUSCULOSKELETAL SYSTEM																					
Heart		N	N	N	N	I	N	N	I	M	M	N	N	N	M	M	N	N	I	0	N
Sternum		N	N	N	I	N	I	N	N	M	M	I	N	N	M	I	N	N	N	0	N

TABLE I (Continued)

INDIVIDUAL ANIMAL HISTOPATHOLOGY DATA

	Group:	I										II									
	Dose:	0 mg/kg										1000 mg/kg									
	Mode of Death:	S	S	S	S	S	S	S	S	S	S	S	S	D	S	S	S	D	D	D	D
	Sex:	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
	Days on Test:	12	12	12	12	12	26	26	26	26	26	12	12	10	12	12	26	8	15	19	8
Tissue*/	Recovery Days:	0	0	0	0	0	14	14	14	14	14	0	0	0	0	0	14	0	3	7	0
Observations**	Rat No. 301-:	544	543	542	541	540	545	546	547	548	549	550	551	552	553	554	555	556	557	558	559
NERVOUS SYSTEM																					
Eyes		M	M	I	M	M	M	M	M	M	M	M	M	M	M	M	M	I	A	O	A
Brain		M	M	M	M	M	I	M	M	M	M	M	M	M	M	M	M	M	A	O	I
RESPIRATORY SYSTEM																					
Trachea		M	M	I	M	M	O	M	M	M	M	L	M	M	M	M	M	M	A	O	A
Tracheitis, lymphocytic, focal		-	-	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-	-	-	-
Lungs		M	L	M	M	L	M	L	L	L	L	M	M	M	L	M	L	M	M	O	M
Pneumonitis, interstitial, granulomatous, multifocal		-	2	-	-	2	-	3	2	2	2	-	-	-	1	-	1	-	-	-	-
UROGENITAL SYSTEM																					
Kidney (s)		L	L	M	M	L	L	L	M	M	M	L	L	L	L	L	L	L	L	O	L
Nephritis, tubulointerstitial, purulent, bilateral multifocal		-	-	-	-	-	-	-	-	-	-	3	3	2	1	2	-	3	3	-	3
Nephritis, lymphocytic, interstitial focal		1	-	-	-	-	1	-	-	-	-	-	-	-	-	-	3	-	-	-	-
Tubular epithelium, basophilia, multifocal or focal		-	1	-	-	1	1	1	-	-	-	-	-	-	-	-	3	-	-	-	-

TABLE I (Continued)

INDIVIDUAL ANIMAL HISTOPATHOLOGY DATA

Part 4

Tissue*/ Observations**	Group:	I										II									
	Dose:	0 mg/kg										1000 mg/kg									
	Mode of Death:	S	S	S	S	S	S	S	S	S	S	S	S	D	S	S	S	D	D	D	D
	Sex:	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
	Days on Test:	12	12	12	12	12	26	26	26	26	26	12	12	10	12	12	26	8	15	19	8
	Recovery Days:	0	0	0	0	0	14	14	14	14	14	0	0	0	0	0	14	0	3	7	0
	Rat No. 301-:	544	543	542	541	540	545	546	547	548	549	550	551	552	553	554	555	556	557	558	559
Nephritis, tubulointerstitial, lymphocytic, neutrophilic, unilateral, multifocal		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Nephrosis, unilateral, multifocal		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Capsulitis, fibrinopurulent, hemorrhagic, unilateral, focal		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Testis (des)		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	0	0
Seminiferous tubular epithelium, atrophy, diffuse, bilateral		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Interstitial cell hyperplasia, diffuse, bilateral		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Epididymis (des)		L	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	0	0
Epididymitis, interstitial, lymphocytic, unilateral, focal		1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

TABLE I (Continued)

INDIVIDUAL ANIMAL HISTOPATHOLOGY DATA

Part 5

Tissues*/ Observations**	Group:	III										IV									
	Dose:	100 mg/kg										10 mg/kg									
	Mode of Death:	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
	Sex:	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
	Days on Test:	12	12	12	12	12	26	26	26	26	26	12	12	12	12	12	26	26	26	26	26
	Recovery Days:	0	0	0	0	0	14	14	14	14	14	0	0	0	0	0	14	14	14	14	14
	Rat No. 301-:	582	583	584	585	586	587	588	589	590	591	592	593	594	595	596	597	598	599	600	601
ENDOCRINE SYSTEM																					
Adrenal Gland (s)		N	N	N	N	N	N	N	N	N	N	I	N	N	N	I	I	I	N	N	I
Thyroid Gland		O	O	O	O	N	N	O	N	N	N	N	N	N	N	N	O	N	O	N	O
Parathyroid Gland (s)		O	O	O	O	O	N	O	O	O	O	O	O	N	O	O	O	O	O	O	O
GASTRO INTESTINAL SYSTEM																					
Esophagus		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Periesophagitis, granulomatous, focal		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Stomach		N	N	I	N	N	N	N	N	N	N	N	N	N	N	N	N	I	N	N	N
Glandular, atrophy, diffuse		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Duodenum		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Ileum		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N
Jejunum		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Cecum		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Colon		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Liver		N	Q	Q	Q	Q	N	N	Q	N	N	Q	Q	N	Q	L	N	Q	L	N	N

TABLE I (Continued)

INDIVIDUAL ANIMAL HISTOPATHOLOGY DATA

Tissue*/ Observation**	Group:	III										IV									
	Dose:	100 mg/kg										10 mg/kg									
	Mode of Death:	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
	Sex:	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
	Days on Test:	12	12	12	12	12	26	26	26	26	26	12	12	12	12	12	26	26	26	26	26
	Recovery Days:	0	0	0	0	0	14	14	14	14	14	0	0	0	0	0	14	14	14	14	14
	Rat No. 301-:	582	583	584	585	586	587	588	589	590	591	592	593	594	595	596	597	598	599	600	601
Hepatitis, necrotic, purulogranulomatous, multifocal		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hepatitis, lymphocytic, focal		-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	1	-	-
HEMOPOIETIC SYSTEM																					
Spleen		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Lymphocytic depletion, diffuse		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bone Marrow		I	I	N	I	I	N	I	I	I	N	N	I	N	I	I	N	N	I	N	I
Hypocellularity, diffuse		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Thymus		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Lymphocytic depletion, diffuse		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Thymusitis, pyogranulomatous, focal		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Thymic Lymph Node		N	N	N	N	N	N	N	N	L	N	N	N	N	O	N	O	N	N	O	N
Lymphocytic hyperplasia, diffuse		-	-	-	-	-	-	-	-	3	-	-	-	-	-	-	-	-	-	-	-
MUSCULOSKELETAL SYSTEM																					
Heart		N	M	I	N	N	N	N	N	N	N	I	N	M	N	N	N	I	N	N	N
Sternum		I	I	N	I	I	N	I	I	I	N	N	I	I	I	I	N	N	I	N	I

TABLE I (Continued)

Part 7

INDIVIDUAL ANIMAL HISTOPATHOLOGY DATA

Tissue*/ Observations**	Group:	III										IV									
	Dose:	100 mg/kg										10 mg/kg									
	Mode of Death:	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
	Sex:	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
	Days on Test:	12	12	12	12	12	26	26	26	26	26	12	12	12	12	12	26	26	26	26	26
	Recovery Days:	0	0	0	0	0	14	14	14	14	14	0	0	0	0	0	14	14	14	14	14
	Rat No. 301-:	582	583	584	585	586	587	588	589	590	591	592	593	594	595	596	597	598	599	600	601
NERVOUS SYSTEM																					
Eyes		N	N	N	N	N	N	N	N	I	N	I	N	N	I	N	N	N	N	N	N
Brain		N	N	N	N	N	N	N	N	N	N	N	N	I	N	N	I	N	I	N	I
RESPIRATORY SYSTEM																					
Trachea		N	I	N	L	L	N	N	N	N	N	N	L	N	N	L	N	N	I	N	N
Trachelitis, lymphocytic, focal		-	-	-	2	1	-	-	-	-	-	-	1	-	-	1	-	-	-	-	-
Lungs		L	M	L	N	N	L	L	L	L	L	L	N	N	N	N	L	N	L	L	L
Pneumonitis interstitial, granulomatous, multifocal		2	-	2	-	-	1	3	2	2	1	2	-	-	-	-	1	-	2	2	1
UROGENITAL SYSTEM																					
Kidney (s)		L	N	N	L	N	N	L	L	L	N	N	L	L	N	N	L	L	L	N	N
Nephritis, tubulointerstitial, purulent, bilateral multifocal		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Nephritis, lymphocytic, interstitial focal		2	-	-	1	-	-	1	:	-	-	-	1	-	-	-	-	1	-	-	-
Tubular epithelium, basophilia, multifocal or focal		2	-	-	-	-	-	-	1	1	-	-	-	-	-	-	1	1	1	-	-

TABLE 1 (Continued)

Part 8

INDIVIDUAL ANIMAL HISTOPATHOLOGY DATA

Tissue*/ Observations**	Group:	III										VI									
	Dose:	100 mg/kg										10 mg/kg									
	Mode of Death:	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
	Sex:	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
	Days on Test:	12	12	12	12	12	26	26	26	26	26	12	12	12	12	12	26	26	26	26	26
	Recovery Days:	0	0	0	0	0	14	14	14	14	14	0	0	0	0	0	14	14	14	14	14
	Rec No. 301-:	582	583	584	585	586	587	588	589	590	591	592	593	594	595	596	597	598	599	600	601
Nephritis, tubulointerstitial, lymphocytic, neutrophilic, unilateral, multifocal		-	-	-	-	-	-	-	-	-	-	-	-	3	-	-	-	-	-	-	-
Nephrosis, unilateral, multifocal		-	-	-	-	-	-	-	-	-	-	-	-	3	-	-	-	-	-	-	-
Capsulitis, fibrinopurulent, hemorrhagic, unilateral, focal		-	-	-	-	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-	-
Testis (es)		N	N	N	N	L	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Seminiferous tubular epithelium, atrophy, diffuse, bilateral		-	-	-	-	5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Interstitial cell hyperplasia, diffuse, bilateral		-	-	-	-	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Epididymis (des)		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Epididymitis, interstitial, lymphocytic, unilateral, focal		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

H-14008 [redacted]

TABLE II

SUMMARY OF HISTOPATHOLOGY DATA

Tissue/Observation	Group:	I		II					III		VI	
	Days on Study:	12	26	8	10	12	15	26	12	26	12	26
	No. of Animals:	5	5	2	1	4	1	1	5	5	5	5
	Sex:	M	M	M	M	M	M	M	M	M	M	M
Esophagus		(4)	(5)	(2)	(1)	(4)	(0)	(1)	(5)	(5)	(5)	(5)
Periesophagitis, granulomatous, focal		0	0	0	0	1	0	0	0	0	0	0
Stomach		(5)	(5)	(1)	(1)	(4)	(0)	(1)	(4)	(5)	(5)	(4)
Glandular, atrophy, diffuse		0	0	0	1	0	0	0	0	0	0	0
Liver		(5)	(5)	(2)	(1)	(4)	(0)	(1)	(5)	(5)	(5)	(5)
Hepatitis, necrotic, purulogranulomatous, multifocal		0	0	0	0	1	0	0	0	0	0	0
Hepatitis, lymphocytic, focal		0	0	0	0	0	0	0	0	0	1	1
Spleen		(5)	(5)	(2)	(1)	(4)	(1)	(1)	(5)	(5)	(5)	(5)
Lymphocytic, depletion, diffuse		0	0	2	1	3	1	0	0	0	0	0
Bone Marrow		(4)	(4)	(2)	(1)	(3)	(0)	(1)	(1)	(2)	(2)	(3)
Hypocellularity, diffuse		0	0	1	1	3	0	0	0	0	0	0
Thymus		(4)	(5)	(2)	(0)	(4)	(1)	(1)	(5)	(5)	(5)	(5)
Lymphocytic depletion, diffuse		0	0	2	0	2	1	0	0	0	0	0
Thymusitis, pyogranulomatous, focal		0	0	0	0	0	0	1	0	0	0	0

() = Number of tissues evaluated

TABLE II (Continued)

Part 2

SUMMARY OF HISTOPATHOLOGY DATA

Group:	I		II					III		IV	
Days on Study:	12	26	8	10	12	15	26	12	26	12	26
No. of Animals:	5	5	2	1	4	1	1	5	5	5	5
Tissue/Observation Sex:	M	M	M	M	M	M	M	M	M	M	M
Lymph Node (Thymic)	(4)	(5)	(2)	(1)	(4)	(0)	(1)	(5)	(5)	(4)	(3)
Lymphocytic hyperplasia, diffuse	0	0	0	0	0	0	0	0	1	0	0
Trachea	(4)	(4)	(1)	(1)	(4)	(0)	(1)	(4)	(5)	(5)	(4)
Tracheitis, lymphocytic, focal	0	0	0	0	1	0	0	2	0	2	0
Lungs	(5)	(5)	(2)	(1)	(4)	(1)	(1)	(5)	(5)	(5)	(5)
Pneumonitis, interstitial, granulomatous, multifocal	2	4	0	0	1	0	1	2	5	1	4
Kidneys	(5)	(5)	(2)	(1)	(4)	(1)	(1)	(5)	(5)	(5)	(5)
Nephritis, tubulointerstitial, purulent, bilateral, multifocal	0	0	2	1	4	1	0	0	0	0	0
Nephritis, lymphocytic, interstitial, focal	1	1	0	0	0	0	1	2	2	1	1
Tubular epithelium, basophilia focal or multifocal	2	2	0	0	0	0	1	1	2	0	3
Nephrosis, multifocal, unilateral	0	0	0	0	0	0	0	0	0	1	0
Capsulitis, fibrinopurient, hemorrhagic, multifocal, unilateral	0	0	0	0	0	0	0	0	0	1	0

() = Number of tissues evaluated

TABLE II (Continued)

SUMMARY OF HISTOPATHOLOGY DATA

Part 3

Group:	I		II					III		IV	
Days on Study:	12	26	8	10	12	15	26	12	26		26
No. of Animals:	5	5	2	1	4	1	1	5	5	5	5
Tissue/Observation Sex:	M	M	M	M	M	M	M	M	M	M	M
Testis (es):	(5)	(5)	(1)	(1)	(4)	(1)	(1)	(5)	(5)	(5)	(5)
Seminiferous tubular epithelium, atrophy, diffuse, bilateral	0	0	0	0	0	0	0	1	0	0	0
Interstitial cell hyperplasia, diffuse, bilateral	0	0	0	0	0	0	0	1	0	0	0
Epididymis (des):											
Epididymitis, interstitial, lymphocytic, focal, unilateral	1	0	0	0	0	0	0	0	0	0	0

() = Number of tissues evaluated

APPENDIX B

E. I. DU PONT DE NEMOURS & COMPANY
(INCORPORATED)
HASKELL LABORATORY FOR TOXICOLOGY
AND INDUSTRIAL MEDICINE
ELKTON ROAD, NEWARK, DELAWARE 19711

CENTRAL RESEARCH AND DEVELOPMENT DEPARTMENT

Subacute Oral Toxicity of [redacted]

Medical Research Project No. [redacted]

Haskell Laboratory No. 14008

June 29, 1981

Blood samples from three groups of 10 male rats intragastrically dosed 10 times with [redacted] at levels of 0 mg/kg (controls), 10 mg/kg and 100 mg/kg and 1 group of 7 male rats dosed with 1000 mg/kg were examined.

After the tenth dose, blood was taken from the tails of these rats for the measurement of erythrocytes (RBC), hemoglobin (Hb), mean corpuscular volume (MCV), platelets, leukocytes (WBC) and relative number of neutrophils (Neut), lymphocytes (Lymph), eosinophils (Eosin), monocytes (Mono) and basophils (Baso). The hematocrit (Ht), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) were calculated from these data. Alkaline phosphatase (AP), glutamic-pyruvic transaminase (GPT), glutamic-oxaloacetic transaminase (GOT), urea nitrogen (BUN), creatinine (CREAT), and total protein (TPROT) were also measured in the serum. Five rats from the 0 mg/kg, 10 mg/kg and 100 mg/kg groups and four rats from the 1000 mg/kg group were then sacrificed for pathology. After a 14-day recovery period, the measurements were repeated on the surviving rats in each group.

The data were analyzed statistically by a one-way analysis of variance. Least significant differences were calculated to compare [redacted] treated rats with the controls when the ratio of variances (F) indicated a difference among the groups. Significance was judged at the 0.05 probability level.

The results of the clinical laboratory measurements are summarized in Table I; statistical analysis in Table II. Measurements on individual animals are listed in the computer printout attached to the report.

Statistical analysis of the data showed that rats dosed 10 times with [redacted] at levels of 100 mg/kg and 1000 mg/kg had higher than normal erythrocyte counts and hematocrits which appeared to be related to the dose. These two groups also had a slightly lower MCH and MCHC when

compared to the control animals. Rats dosed with 1000 mg/kg [redacted] had higher leukocyte counts, almost twice the normal range established by the controls. These animals also showed a three-fold increase in serum BUN and increased hemoglobin, GPT and creatinine. The 100 mg/kg treated rats showed a slight increase in serum total protein. Examination of the differential smears showed an increase in the relative number of neutrophils in the 1000 mg/kg group and a slight to moderate hypochromia in the 100 mg/kg and 1000 mg/kg groups.

Fourteen days later, only one rat remained in the 1000 mg/kg [redacted] treated group. Statistical analysis at this time included the control, 10 mg/kg and 100 mg/kg dose levels. Other than a slight increase in serum creatinine levels in the 100 mg/kg-treated rats, no clinically significant difference between the control rats and [redacted] treated rats was found for the other measurements made on the blood.

Report by: Catherine C. Matarese
Catherine C. Matarese
Technician

Approved by: John R Barnes
John R. Barnes
Chief,
Clinical Pathology Section

CCM:JRB:mjh

TABLE I

AVERAGE CLINICAL LABORATORY VALUES ON RATS INTUBATED WITH [redacted]

	10 DAY				RECOVERY			
	0 mg/kg	10 mg/kg	100 mg/kg	1000 mg/kg	0 mg/kg	10 mg/kg	100 mg/kg	1000 mg/kg*
Erythrocytes $10^6/mm^3$	6.64	6.64	7.21	8.11	7.01	6.93	6.98	6.25
Hemoglobin g%	15.3	15.1	15.9	17.6	15.4	15.3	15.4	14.1
Hematocrit %	38	38	41	48	40	39	40	37
MCV μ^3	58	57	57	59	57	57	57	59
MCH pg	23	23	22	22	22	22	22	23
MCHC %	40	40	40	37	38	39	39	38
Platelet $10^3/mm^3$	1066	1069	1198	1028	1070	1075	1190	1214
Leukocytes $10^3/mm^3$	12.9	12.3	14.0	23.0	13.2	10.5	13.7	12.6
Neutrophils	17	16	11	38	16	20	15	22
Lymphocytes	75	79	84	53	80	73	81	67
Eosinophils	0.5	0.3	0.3	0.9	0.6	1.0	0.2	1.0
Monocytes	5.3	5.2	4.4	8.6	3.8	6.4	3.6	10.0
Basophils	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AP IU	258	203	246	291	276	217	243	245
GPT IU	19	19	20	23	20	18	19	14
GOT IU	53	51	56	60	47	52	44	25
BUN mg/dl	20	21	21	78	20	18	19	29
CREAT mg/dl	0.6	0.6	0.6	1.0	0.6	0.6	0.7	0.6
TPROT g/dl	5.9	5.8	6.1	5.8	6.3	6.2	6.4	6.4

* = only one rat survived the recovery period

TABLE II

SUMMARY OF STATISTICAL ANALYSIS ON RATS INTUBATED WITH [redacted]

		10 DAY			RECOVERY		
	F*	10 mg/kg	100 mg/kg	1000 mg/kg	F#	10 mg/kg	100 mg/kg
RBC	23.)	0	+	+	0.1	0	0
Hb	13.1	0	0	+	0.0	0	0
Ht	30.4	0	+	+	0.4	0	0
MCV	3.4	0	0	0	0.2	0	0
MCH	5.2	0	-	-	0.1	0	0
MCHC	18.1	0	-	-	1.4	0	0
Platelet	1.9	0	0	0	2.0	0	0
WBC	9.4	0	0	+	2.9	0	0
Neut	24.1	0	0	+	0.9	0	0
Lymph	15.7	0	+	-	1.8	0	0
Eosin	1.0	0	0	0	2.4	0	0
Mono	5.3	0	0	+	1.6	0	0
AP	5.5	-	0	0	6.4	-	0
GPT	3.8	0	0	+	0.3	0	0
GOT	1.6	0	0	0	0.5	0	0
BUN	122.0	0	0	+	0.7	0	0
CREAT	34.2	0	0	+	10.0	0	+
TPROT	5.2	0	+	0	2.3	0	0

F = Ratio of variance

F* = Significant if > 2.89

F# = Significant if > 3.88

(0) = Not significantly different than controls

(+) = Significantly higher than controls

(-) = Significantly lower than controls

MR: [redacted] HASKELL#: 14008 HASKELL CODE#: [redacted]
COMPND: [redacted]
PERIOD: 10 DAY DPRTMNT: PPD&CP
TOXICOLOGIST: DASHIEL REPORT DATE: 18-May-81
CLINICAL LAB: MATARESE

GROUP: 1CM DOSE: CONTROL SEX: MALE SPECIES: RAT
SAMPLE DATE: 15-MAY-81 BIRTH DATE: 13-MAR-81

ANIMAL#:	RBC MM/cm	Hb g%	Ht %	MCV /cmc	MCH /mmg	MCHC %	PLAT M/cmm
301540	6.91	15.2	38.	55.	22.	40.	1071.
301541	6.67	15.2	39.	58.	23.	39.	1058.
301542	6.41	14.6	37.	58.	23.	40.	1005.
301543	6.64	15.9	38.	58.	24.	41.	898.
301544	6.77	15.1	38.	57.	22.	39.	1180.
301545	6.35	14.1	36.	57.	22.	39.	1167.
301546	6.47	15.3	38.	58.	24.	41.	972.
301547	6.87	15.8	41.	59.	23.	39.	1080.
301548	6.86	16.0	40.	59.	23.	40.	1061.
301549	6.46	15.4	37.	57.	24.	42.	1163.
AVG.	6.641	15.26	38.2	57.6	23.0	40.0	1065.5
S. D.	0.208	0.59	1.5	1.2	0.8	1.1	90.5
S. E.	0.066	0.19	0.5	0.4	0.3	0.3	28.6

GROUP: 2M DOSE: 1000 MG/KG SEX: MALE SPECIES: RAT
SAMPLE DATE: 15-MAY-81 BIRTH DATE: 13-MAR-81

ANIMAL#:	RBC MM/cm	Hb g%	Ht %	MCV /cmc	MCH /mmg	MCHC %	PLAT M/cmm
301550	7.57	16.5	45.	59.	22.	37.	1351.
301551	7.21	15.4	43.	59.	21.	36.	797.
301553	8.53	18.3	50.	59.	21.	37.	822.
301554	8.29	17.8	49.	59.	22.	36.	1210.
301555	7.66	16.8	45.	58.	22.	38.	888.
301557	9.29	20.5	55.	59.	22.	37.	1329.
301558	8.25	18.1	47.	57.	22.	38.	802.
AVG.	8.114	17.63	47.7	58.6	21.7	37.0	1028.4
S. D.	0.698	1.63	4.0	0.8	0.5	0.8	256.4
S. E.	0.264	0.61	1.5	0.3	0.2	0.3	96.9

MR: [redacted] HASKELL#: 14008 HASKELL CODE#: [redacted]
COMPND: [redacted]
PERIOD: 90 DAY DPRTMNT: PPD&CP
TOXICOLOGIST: DASHIELL REPORT DATE: 9-Jun-81
CLINICAL LAB: MATARESE

GROUP: 1CM DOSE: CONTROL SEX: MALE SPECIES: RAT
SAMPLE DATE: 15-MAY-81 BIRTH DATE: 13-MAR-81

ANIMAL#:	WBC M/cm	Neut %	Lymph %	Eosin %	Mono %	Baso %
301540	17.9	18.	76.	0.	6.	0.
301541	11.6	19.	75.	0.	6.	0.
301542	12.5	15.	82.	0.	3.	0.
301543	9.6	19.	73.	1.	7.	0.
301544	12.0	17.	78.	0.	5.	0.
301545	13.5	17.	48.	1.	4.	0.
301546	11.1	19.	76.	1.	4.	0.
301547	11.3	19.	77.	1.	3.	0.
301548	13.5	12.	80.	1.	7.	0.
301549	15.8	12.	80.	0.	8.	0.
AVG.	12.88	16.7	74.5	0.5	5.3	0.0
S. D.	2.44	2.8	9.7	0.5	1.8	0.0
S. E.	0.77	0.9	3.1	0.2	0.6	0.0

GROUP: 2M DOSE: 1000 MG/KG SEX: MALE SPECIES: RAT
SAMPLE DATE: 15-MAY-81 BIRTH DATE: 13-MAR-81

ANIMAL#:	WBC M/cm	Neut %	Lymph %	Eosin %	Mono %	Baso %
301550	40.4	36.	56.	0.	8.	0.
301551	20.8	34.	57.	0.	9.	0.
301553	16.2	24.	71.	1.	4.	0.
301554	18.2	29.	61.	0.	10.	0.
301555	20.6	32.	63.	0.	5.	0.
301557	16.5	63.	22.	3.	12.	0.
58	28.6	45.	41.	2.	12.	0.
n .	23.04	37.6	53.0	0.9	8.6	0.0
S. D.	8.72	12.9	16.4	1.2	3.2	0.0
S. E.	3.30	4.9	6.2	0.5	1.2	0.0

MR: [redacted] HASKELL#: 14008 HASKELL CODE#: [redacted]
COMPND: [redacted] DPRTMNT: PPD&CP
PERIOD: 10 DAY REPORT DATE: 9-Jun-81
TOXICOLOGIST: DASHIELL CLINICAL LAB: MATARESE

GROUP: 3M DOSE: 100 MG/KG SEX: MALE SPECIES: RAT
SAMPLE DATE: 15-MAY-81 BIRTH DATE: 13-MAR-81

ANIMAL#:	WBC M/cm	Neut %	Lymph %	Eosin %	Mono %	Baso %
301582	9.7	18.	74.	0.	8.	0.
301583	14.3	14.	79.	0.	7.	0.
301584	13.8	13.	83.	1.	3.	0.
301585	9.0	10.	88.	0.	2.	0.
301586	14.6	5.	88.	1.	6.	0.
301587	10.7	11.	87.	0.	2.	0.
301588	19.7	12.	84.	0.	4.	0.
301589	15.8	11.	84.	0.	5.	0.
301590	17.5	10.	85.	1.	4.	0.
301591	15.2	6.	91.	0.	3.	0.
AVG.	14.03	11.0	84.3	0.3	4.4	0.0
S. D.	3.40	3.7	4.9	0.5	2.1	0.0
S. E.	1.08	1.2	1.5	0.2	0.7	0.0

GROUP: 4M DOSE: 10 MG/KG SEX: MALE SPECIES: RAT
SAMPLE DATE: 15-MAY-81 BIRTH DATE: 13-MAR-81

ANIMAL#:	WBC M/cm	Neut %	Lymph %	Eosin %	Mono %	Baso %
301592	14.9	12.	85.	0.	3.	0.
301593	17.6	10.	86.	0.	4.	0.
301594	13.9	22.	69.	0.	9.	0.
301595	10.4	16.	81.	0.	3.	0.
301596	10.5	22.	72.	2.	4.	0.
301597	10.3	14.	82.	0.	4.	0.
301598	9.5	9.	85.	0.	6.	0.
301599	10.6	14.	80.	0.	6.	0.
301600	10.4	15.	76.	1.	8.	0.
301601	14.6	25.	70.	0.	5.	0.
AVG.	12.27	15.9	78.6	0.3	5.2	0.0
S. D.	2.75	5.4	6.4	0.7	2.0	0.0
S. E.	0.87	1.7	2.0	0.2	0.6	0.0

MR: [redacted] HASKELL#: 14008 HASKELL CODE#: [redacted]
COMPND: [redacted]
PERIOD: RECOVERY DPRTMNT: PPD&CP
TOXICOLOGIST: DASHIEL REPORT DATE: 1-Jun-81
CLINICAL LAB: MATARESE

GROUP: 1CM DOSE: CONTROL SEX: MALE SPECIES: RAT
SAMPLE DATE: 29-MAY-81 BIRTH DATE: 13-MAR-81

ANIMAL#:	RBC MM/cm	Hb g%	Ht %	MCV /cmc	MCH /mmg	MCHC %	PLAT M/cmm
301540							
301541							
301542							
301543							
301544							
301545	7.53	15.9	42.	55.	21.	38.	1220.
301546	6.35	14.2	36.	57.	22.	40.	1062.
301547	7.02	16.2	43.	61.	23.	38.	944.
301548	7.11	15.6	41.	57.	22.	38.	1142.
301549	7.02	15.2	40.	57.	22.	38.	980.
AVG.	7.006	15.42	40.4	57.4	22.0	38.4	1069.6
S. D.	0.423	0.78	2.7	2.2	0.7	0.9	113.7
S. E.	0.189	0.35	1.2	1.0	0.3	0.4	50.9

GROUP: 2M DOSE: 1000 MG/KG SEX: MALE SPECIES: RAT
SAMPLE DATE: 29-MAY-81 BIRTH DATE: 13-MAR-81

ANIMAL#:	RBC MM/cm	Hb g%	Ht %	MCV /cmc	MCH /mmg	MCHC %	PLAT M/cmm
301550							
301551							
301553							
301554							
301555	6.25	14.1	37.	59.	23.	38.	1214.
301557							
301558							
AVG.	6.250	14.10	37.0	59.0	23.0	38.0	1214.0
S. D.							
S. E.							

MR: [redacted] HASKELL#: 14008 HASKELL CODE#: [redacted]
COMPND: [redacted]
PERIOD: 90 DAY DPRTMNT: PPD&CP
TOXICOLOGIST: DASHIEL REPORT DATE: 18-May-81
CLINICAL LAB: MATARESE

GROUP: 3M DOSE: 100 MG/KG SEX: MALE SPECIES: RAT
SAMPLE DATE: 15-MAY-81 BIRTH DATE: 13-MAR-81

ANIMAL#:	AP IU	GPT IU	GOT IU	BUN mg%	CREAT mg%	TPROT g%
301582	225.	23.	70.	25.0	0.6	6.2
301583	235.	25.	75.	24.0	0.3	5.7
301584	180.	14.	40.	20.0	0.6	6.0
301585	285.	19.	50.	24.0	0.6	5.7
301586	220.	21.	50.	19.0	0.6	6.2
301587	230.	16.	60.	21.0	0.5	6.1
301588	330.	19.	50.	21.0	0.6	6.4
301589	290.	25.	65.	20.0	0.6	6.3
301590	240.	19.	50.	18.0	0.5	6.3
301591	225.	19.	45.	20.0	0.6	6.3
AVG.	246.0	20.0	55.5	21.20	0.56	6.12
S. D.	43.3	3.6	11.4	2.35	0.10	0.25
S. E.	13.7	1.1	3.6	0.74	0.03	0.08

GROUP: 4M DOSE: 10 MG/KG SEX: MALE SPECIES: RAT
SAMPLE DATE: 15-MAY-81 BIRTH DATE: 13-MAR-81

ANIMAL#:	AP IU	GPT IU	GOT IU	BUN mg%	CREAT mg%	TPROT g%
301592	145.	17.	50.	20.0	0.5	6.1
301593	280.	17.	50.	19.0	0.5	5.8
301594	170.	19.	60.	25.0	0.6	5.8
301595	195.	17.	55.	21.0	0.7	6.1
301596	230.	21.	55.	22.0	0.5	5.8
301597	170.	19.	45.	20.0	0.6	5.7
301598	205.	21.	45.	18.0	0.6	5.9
301599	185.	19.	50.	21.0	0.7	5.5
301600	250.	21.	55.	17.0	0.5	5.7
301601	200.	19.	45.	22.0	0.6	5.6
AVG.	203.0	19.0	51.0	20.50	0.59	5.80
S. D.	40.6	1.6	5.2	2.27	0.06	0.19
S. E.	12.8	0.5	1.6	0.72	0.02	0.06

MR: [redacted] HASKELL#: 14008 HASKELL CODE#: [redacted]
COMPND: [redacted] DPRTMNT: PPD&CP
PERIOD: 10 DAY REPORT DATE: 18-May-81
TOXICOLOGIST: DASHIEL CLINICAL LAB: MATARESE

GROUP: 1CM DOSE: CONTROL SEX: MALE SPECIES: RAT
SAMPLE DATE: 15-MAY-81 BIRTH DATE: 13-MAR-81

ANIMAL#:	AP IU	GPT IU	GOT IU	BUN mg%	CREAT mg%	TPROT g%
301540	195.	16.	50.	22.0	0.7	5.8
301541	255.	19.	65.	22.0	0.5	5.8
301542	265.	19.	45.	18.0	0.7	5.7
301543	265.	23.	60.	21.0	0.6	5.9
301544	185.	19.	50.	19.0	0.6	5.5
301545	265.	17.	60.	20.0	0.7	5.9
301546	325.	19.	50.	21.0	0.6	6.0
301547	280.	17.	45.	19.0	0.7	6.2
301548	240.	19.	50.	20.0	0.6	6.0
301549	300.	21.	55.	21.0	0.5	5.9
AVG.	257.5	18.9	53.0	20.30	0.62	5.87
S. D.	42.8	2.0	6.7	1.34	0.06	0.19
S. E.	13.5	0.6	2.1	0.42	0.02	0.06

GROUP: 2M DOSE: 1000 MG/KG SEX: MALE SPECIES: RAT
SAMPLE DATE: 15-MAY-81 BIRTH DATE: 13-MAR-81

ANIMAL#:	AP IU	GPT IU	GOT IU	BUN mg%	CREAT mg%	TPROT g%
301550	290.	19.	45.	74.0	1.1	5.8
301551	395.	28.	65.	61.0	1.0	5.5
301553	305.	19.	55.	66.0	0.9	5.8
301554	240.	25.	60.	79.0	1.2	6.2
301555	315.	28.	75.	91.0	1.3	5.5
301557	210.	25.	70.	106.0	0.9	5.7
301558	285.	19.	50.	66.0	0.8	5.8
AVG.	291.4	23.3	60.0	77.57	1.02	5.76
S. D.	58.9	4.2	10.8	16.05	0.18	0.24
S. E.	22.2	1.6	4.1	6.07	0.07	0.09

MR: [redacted] HASKELL#: 14008 HASKELL CODE#: [redacted]
COMPND: [redacted]
PERIOD: 10 DAY DPRTMNT: PPD&CP
TOXICOLOGIST: DASHIEL REPORT DATE: 18-May-81
CLINICAL LAB: MATARESE

GROUP: 3M DOSE: 100 MG/KG SEX: MALE SPECIES: RAT
SAMPLE DATE: 15-MAY-81 BIRTH DATE: 13-MAR-81

ANIMAL#:	RBC MM/cm	Hb g%	Ht %	MCV /cmc	MCH /mmg	MCHC %	PLAT M/cmm
301582	7.49	16.2	42.	55.	22.	39.	1021.
301583	7.01	16.0	42.	60.	23.	38.	1322.
301584	6.72	15.0	37.	55.	22.	40.	1307.
301585	7.27	15.5	40.	55.	21.	39.	1089.
301586	7.20	15.8	41.	57.	22.	38.	1191.
301587	6.65	14.6	38.	57.	22.	38.	1021.
301588	7.79	16.6	43.	55.	21.	39.	1503.
301589	7.41	17.0	42.	57.	23.	40.	1152.
301590	7.49	16.9	43.	58.	23.	39.	1157.
301591	7.10	15.5	40.	57.	22.	39.	1217.
AVG.	7.213	15.91	40.8	56.6	22.1	38.9	1198.0
S. D.	0.356	0.79	2.0	1.6	0.7	0.7	148.7
S. E.	0.113	0.25	0.6	0.5	0.2	0.2	47.0

GROUP: 4M DOSE: 10 MG/KG SEX: MALE SPECIES: RAT
SAMPLE DATE: 15-MAY-81 BIRTH DATE: 13-MAR-81

ANIMAL#:	RBC MM/cm	Hb g%	Ht %	MCV /cmc	MCH /mmg	MCHC %	PLAT M/cmm
301592	6.78	14.9	38.	56.	22.	39.	1226.
301593	6.84	14.9	38.	55.	22.	39.	1268.
301594	6.21	14.2	35.	56.	23.	41.	983.
301595	6.89	15.6	39.	57.	23.	40.	972.
301596	6.64	15.6	39.	59.	24.	40.	992.
301597	6.76	14.5	38.	56.	22.	39.	913.
301598	7.10	15.6	40.	56.	22.	39.	944.
301599	6.12	15.0	36.	59.	25.	42.	898.
301600	6.63	15.4	39.	58.	23.	40.	1262.
301601	6.41	14.9	37.	58.	23.	40.	1231.
AVG.	6.638	15.06	37.9	57.0	22.9	39.9	1068.9
S. D.	0.308	0.49	1.5	1.4	1.0	1.0	156.2
S. E.	0.098	0.15	0.5	0.4	0.3	0.3	49.4

MR: [redacted] HASKELL#: 14008 HASKELL CODE#: [redacted]
COMPND: [redacted]
PERIOD: RECOVERY DPRTMNT: PPD&CP
TOXICOLOGIST: DASHIEL REPORT DATE: 1-Jun-81
CLINICAL LAB: MATARESE

GROUP: 3M DOSE: 100 MG/KG SEX: MALE SPECIES: RAT
SAMPLE DATE: 29-MAY-81 BIRTH DATE: 13-MAR-81

ANIMAL#:	RBC MM/cm	Hb g%	Ht %	MCV /cmc	MCH /mmg	MCHC %	PLAT M/cmm
301582							
301583							
301584							
301585							
301586							
301587	6.90	15.4	40.	58.	22.	39.	1142.
301588	7.18	15.1	39.	54.	21.	39.	1292.
301589	6.80	15.4	39.	58.	23.	39.	1260.
301590	6.69	15.3	39.	59.	23.	39.	1020.
301591	7.31	16.0	41.	56.	22.	39.	1238.
AVG.	6.976	15.44	39.6	56.8	22.2	39.0	1190.4
S. D.	0.261	0.34	0.9	2.2	0.8	0.0	110.5
S. E.	0.117	0.15	0.4	1.0	0.4	0.0	49.4

GROUP: 4M DOSE: 10 MG/KG SEX: MALE SPECIES: RAT
SAMPLE DATE: 29-MAY-81 BIRTH DATE: 13-MAR-81

ANIMAL#:	RBC MM/cm	Hb g%	Ht %	MCV /cmc	MCH /mmg	MCHC %	PLAT M/cmm
301592							
301593							
301594							
301595							
301596							
301597	7.11	15.4	39.	55.	22.	39.	980.
301598	6.85	15.0	38.	56.	22.	39.	986.
301599	6.86	15.2	39.	57.	22.	39.	1066.
301600	7.44	16.4	43.	58.	22.	38.	1204.
301601	6.40	14.7	37.	57.	23.	40.	1138.
AVG.	6.932	15.34	39.2	56.6	22.2	39.0	1074.8
S. D.	0.382	0.65	2.3	1.1	0.4	0.7	97.0
S. E.	0.171	0.29	1.0	0.5	0.2	0.3	43.4

MR: [redacted] HASKELL#: 14008 HASKELL CODE#: [redacted]
COMPND: [redacted]
PERIOD: RECOVERY DPRTMNT: PPD&CP
TOXICOLOGIST: DASHIELL REPORT DATE: 9-Jun-81
CLINICAL LAB: MATARESE

GROUP: 1CM DOSE: CONTROL SEX: MALE SPECIES: RAT
SAMPLE DATE: 29-MAY-81 BIRTH DATE: 13-MAR-81

ANIMAL#:	WBC M/cm	Neut %	Lymph %	Eosin %	Mono %	Baso %
301540						
301541						
301542						
301543						
301544						
301545	12.3	12.	84.	0.	4.	0.
301546	15.4	29.	67.	1.	3.	0.
301547	10.3	13.	82.	0.	5.	0.
301548	14.9	20.	75.	1.	4.	0.
301549	13.2	6.	90.	1.	3.	0.
AVG.	13.22	16.0	79.6	0.6	3.8	0.0
S. D.	2.06	8.8	8.8	0.5	0.8	0.0
S. E.	0.92	3.9	4.0	0.2	0.4	0.0

GROUP: 2M DOSE: 1000 MG/KG SEX: MALE SPECIES: RAT
SAMPLE DATE: 29-MAY-81 BIRTH DATE: 13-MAR-81

ANIMAL#:	WBC M/cm	Neut %	Lymph %	Eosin %	Mono %	Baso %
301550						
301551						
301553						
301554						
301555	12.6	22.	67.	1.	10.	0.
301557						
301558						
AVG.	12.60	22.0	67.0	1.0	10.0	0.0
S. D.						
S. E.						

MR: [redacted] HASKELL#: 14008 HASKELL CODE#: [redacted]
COMPND: [redacted]
PERIOD: RECOVERY DPRTMNT: PPD&CP
TOXICOLOGIST: DASHIELL REPORT DATE: 9-Jun-81
CLINICAL LAB: MATARESE

GROUP: 3M DOSE: 100 MG/KG SEX: MALE SPECIES: RAT
SAMPLE DATE: 29-MAY-81 BIRTH DATE: 13-MAR-81

ANIMAL#:	WBC M/cm	Neut %	Lymph %	Eosin %	Mono %	Baso %
301582						
301583						
301584						
301585						
301586						
301587	13.1	9.	87.	1.	3.	0.
301588	18.6	15.	81.	0.	4.	0.
301589	15.2	17.	80.	0.	3.	0.
301590	10.8	19.	75.	0.	6.	0.
301591	10.9	14.	84.	0.	2.	0.
AVG.	13.72	14.8	81.4	0.2	3.6	0.0
S. D.	3.27	3.8	4.5	0.4	1.5	0.0
S. E.	1.46	1.7	2.0	0.2	0.7	0.0

GROUP: 4M DOSE: 10 MG/KG SEX: MALE SPECIES: RAT
SAMPLE DATE: 29-MAY-81 BIRTH DATE: 13-MAR-81

ANIMAL#:	WBC M/cm	Neut %	Lymph %	Eosin %	Mono %	Baso %
301592						
301593						
301594						
301595						
301596						
301597	10.4	23.	74.	1.	2.	0.
301598	10.4	14.	82.	1.	3.	0.
301599	9.3	15.	76.	1.	8.	0.
301600	12.0	27.	58.	2.	13.	0.
301601	10.2	21.	73.	0.	6.	0.
AVG.	10.46	20.0	72.6	1.0	6.4	0.0
S. D.	0.97	5.5	8.9	0.7	4.4	0.0
S. E.	0.44	2.4	4.0	0.3	2.0	0.0

MR: [redacted] HASKELL#: 14008 HASKELL CODE#: [redacted]
COMPND: [redacted]
PERIOD: RECOVERY DPRTMNT: PPD&CP
TOXICOLOGIST: DASHIEL REPORT DATE: 29-May-81
CLINICAL LAB: MATARESE

GROUP: 1CM DOSE: CONTROL SEX: MALE SPECIES: RAT
SAMPLE DATE: 29-MAY-81 BIRTH DATE: 13-MAR-81

ANIMAL#:	AP IU	GPT IU	GOT IU	BUN mg%	CREAT mg%	TPROT g%
301540						
301541						
301542						
301543						
301544						
301545	290.	17.	35.	22.0	0.6	6.3
301546	300.	19.	35.	18.0	0.6	6.1
301547	275.	17.	35.	19.0	0.6	6.5
301548	225.	21.	60.	18.0	0.6	6.3
301549	290.	25.	70.	22.0	0.7	6.3
AVG.	276.0	19.8	47.0	19.80	0.62	6.30
S. D.	29.9	3.3	16.8	2.05	0.02	0.14
S. E.	13.4	1.5	7.5	0.92	0.01	0.06

GROUP: 2M DOSE: 1000 MG/KG SEX: MALE SPECIES: RAT
SAMPLE DATE: 29-MAY-81 BIRTH DATE: 13-MAR-81

ANIMAL#:	AP IU	GPT IU	GOT IU	BUN mg%	CREAT mg%	TPROT g%
301550						
301551						
301553						
301554						
301555	245.	14.	25.	29.0	0.6	6.4
301557						
301558						
AVG.	245.0	14.0	25.0	29.00	0.64	6.40
S. D.						
S. E.						

MR: [redacted]
COMPND: [redacted]
PERIOD: RECOVERY
TOXICOLOGIST: DASHIEL

HASKELL#: 14008
HASKELL CODE#: [redacted]
DPRTMNT: PPD&CP
REPORT DATE: 29-May-81
CLINICAL LAB: MATARESE

GROUP: 3M DOSE: 100 MG/KG SEX: MALE SPECIES: RAT
SAMPLE DATE: 29-MAY-81 BIRTH DATE: 13-MAR-81

ANIMAL#:	AP IU	GPT IU	GOT IU	BUN mg%	CREAT mg%	TPROT g%
301582						
301583						
301584						
301585						
301586						
301587	240.	14.	60.	15.0	0.8	6.1
301588	275.	21.	35.	20.0	0.7	6.5
301589	245.	25.	50.	19.0	0.8	6.6
301590	240.	16.	40.	18.0	0.6	6.4
301591	215.	17.	35.	21.0	0.7	6.5
AVG.	243.0	18.6	44.0	18.60	0.72	6.42
S. D.	21.4	4.4	10.8	2.30	0.05	0.19
S. E.	9.6	2.0	4.8	1.03	0.02	0.09

GROUP: 4M DOSE: 10 MG/KG SEX: MALE SPECIES: RAT
SAMPLE DATE: 29-MAY-81 BIRTH DATE: 13-MAR-81

ANIMAL#:	AP IU	GPT IU	GOT IU	BUN mg%	CREAT mg%	TPROT g%
301592						
301593						
301594						
301595						
301596						
301597	180.	17.	60.	15.0	0.6	6.1
301598	240.	19.	50.	19.0	0.6	6.0
301599	210.	17.	50.	18.0	0.6	6.1
301600	245.	21.	60.	18.0	0.5	6.5
301601	210.	17.	40.	21.0	0.7	6.2
AVG.	217.0	18.2	52.0	18.20	0.59	6.18
S. D.	26.4	1.8	8.4	2.17	0.06	0.19
S. E.	11.8	0.8	3.7	0.97	0.03	0.09

2-48 REV 12-79

APPENDIX C

[redacted]

E. I. DU PONT DE NEMOURS & COMPANY
INCORPORATED
WILMINGTON, DELAWARE 19898

POLYMER PRODUCTS DEPARTMENT
EXPERIMENTAL STATION

ANALYTICAL REPORT

September 16, 1981

[redacted]
CENTRAL RESEARCH AND DEVELOPMENT
HASKELL LAB

DETERMINATION OF FLUORINE IN RAT BLOOD
(Job No. 812-668; PRAL Nos. 81-2101-2119,81-2419-2434,81-2611-2612;
[redacted]

As part of studies [redacted] (exposure of rats to [redacted] the 37 rat blood samples submitted 5/20/81 - 6/11/81 have been analyzed for fluorine by the Wickbold Torch procedure. The analyses were done by Erik Kissa at Jackson Lab (after preliminary freeze-drying here), and results are given in the attached copy of his report.

S. S. Stafford

Attachments
jah

Key Words:
Fluorine
[redacted]
Blood Analysis
Wickbold Torch

CH-1983 REV. 8-80

[redacted]

E. I. DU PONT DE NEMOURS & COMPANY
INCORPORATED
WILMINGTON, DELAWARE 19898

CHEMICALS AND PIGMENTS DEPARTMENT
JACKSON LABORATORY

September 1, 1981

Sally S. Stafford
Polymers & Plastics Department
Experimental Station 269/212

FLUORINE IN RAT BLOOD CONTAINING [redacted]

The fluorine content of dried rat blood was determined by the oxyhydrogen torch method calibrated with p-fluorobenzoic acid (corrected for a blank and adjusted to 100% fluorine recovery). The results (see attached pages) suggest that the [redacted] recovery rate is similar to that of [redacted]:

Amount of [redacted] ed, mg/kg	Average F ppm Date Sampled 5/15	5/29
1000	197	25*
100	79	25
10	30	12
0	0.9	0.5

*Only one rat survived

Two fluorine values, seemingly out of line, were confirmed by duplicate analyses. The standard deviation of the fluorine content of blood is larger than that of the analytical method, indicating a large variat on of fluorine in blood from rat to rat. We need only about .8-1 mL blood for analyses. If a rat can donate this amount and recover, it may be better to sample the same rat periodically to follow the decrease of fluorine in blood with time.

E. Kissa
Physical & Analytical

EK:mml

Attach.

FLUORINE IN RAT BLOOD CONTAINING [redacted]

Sample Designation (a) PRAL No.	Date Received	Rat #,	Group,	Tube #	Fluorine Content, mg/kg F (b)	Group Average
81-2101	5/20/81	301540	I	Tube 1	1.3	
81-2102	5/20/81	301541	I	Tube 2	1.2	$\bar{X}$ = 0.94
81-2103	5/20/81	301542	I	Tube 3	1.4	σ = 0.52
81-2104	5/20/81	301543	I	Tube 4	0.6	
81-2105	5/20/81	301545	I	Tube 5	0.2	
81-2106	5/20/81	301550	II	Tube 6	212	
81-2107	5/20/81	301551	II	Tube 7	190	$\bar{X}$ = 197
81-2108	5/20/81	301553	II	Tube 8	172	σ = 19.6
81-2109	5/20/81	301554	II	Tube 9	213	
81-2110	5/20/81	301582	III	Tube 10	81	
81-2111	5/20/81	301583	III	Tube 11	79	$\bar{X}$ = 79.4
81-2112	5/20/81	301584	III	Tube 12	78	σ = 2.7
81-2113	5/20/81	301585	III	Tube 13	83	
81-2114	5/20/81	301586	III	Tube 14	76	
81-2115	5/20/81	301592	IV	Tube 15	25.6	
81-2116	5/20/81	301593	IV	Tube 16	31.3, 29.8 Avg. 30.6	$\bar{X}$ = 23.5
81-2117	5/20/81	301594	IV	Tube 17	16.7	σ = 5.1
81-2118	5/20/81	301595	IV	Tube 18	22.8	
81-2119	5/20/81	301596	IV	Tube 19	21.7	
81-2419	6/1/81	303545	I	Tube 1	0.1	
81-2420	6/1/81	303546	I	Tube 2	1.0	$\bar{X}$ = 0.48
81-2421	6/1/81	303547	I	Tube 3	0.5	σ = 0.34
81-2422	6/1/81	303548	I	Tube 4	0.5	
81-2423	6/1/81	303549	I	Tube 5	0.3	
81-2424	6/1/81	301555	II	Tube 6	23.1, 26.9 Avg. 25.	

FLUORINE IN RAT BLOOD CONTAINING [redacted]

Sample Designation (a) PRAL No.	Date Received	Rat #,	Group,	Tube #	Fluorine Content, mg/kg F (b)	Group Average
81-2425	6/1/81	301587	III	Tube 7	20.4	
81-2426	6/1/81	301588	III	Tube 8	31.0	$\bar{X}$ = 25.1
81-2427	6/1/81	301589	III	Tube 9	22.8	σ = 4.2
81-2428	6/1/81	301590	III	Tube 10	27.7	
81-2429	6/1/81	301591	III	Tube 11	23.6	
81-2430	6/1/81	301597	IV	Tube 12	5.4	
81-2431	6/1/81	301598	IV	Tube 13	9.2	$\bar{X}$ = 11.8
81-2432	6/1/81	301599	IV	Tube 14	11.8	σ = 5.0
81-2433	6/1/81	301600	IV	Tube 15	18.6	
81-2434	6/1/81	301601	IV	Tube 16	14.0	
81-2611	6/11/81	304272	Blank		0.0	
81-2612	6/11/81	304273	Blank		0.2	

(a) Sample Designation for [redacted]

Group I - control
Group II = high, 1000 mg/kg
Group III = intermediate, 100 mg/kg
Group IV = low, 10 mg/kg

For samples 81-2101 through -2119, recovery time was 4 hours, after the final dose 5/15/81. For samples 81-2419 through -2434, recovery time was 14 days.

Samples 81-2611 and 81-2612 were "blanks", blood from stock rats not part of the study but dried and analyzed along with the others.

(b) Total fluorine content, not corrected for inorganic fluorine values which are probably insignificant.