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E. I. du Pont de Nemours and Company
Haskell Laboratory for Toxicology and Industrial Medicine

HASKELL LABORATORY REPORT NO. 718-78 [REDACTED]

<u>Material Tested*</u>	<u>Haskell No.</u>	<u>Other Codes</u>	<u>Sample Ready for Testing</u>	<u>Submitted by</u>
[REDACTED]	12,400	[REDACTED]	7-10-78	[REDACTED] CD&P Department, Jackson Lab., Chambers Works

TEN-DOSE ORAL SUBACUTE TEST
[REDACTED]

Procedure: The test material, as an aqueous solution, was administered by intragastric intubation to a group of ten young adult Chr-CD male rats, five times a week for two weeks, at a repeated dosage level of 4,470 mg/kg/day; an additional group of ten rats served as controls and was intubated with distilled water. Five controls and five test rats were sacrificed approximately two-four hours after the last dose. The remaining five control and five test rats were sacrificed 14 days after the last dose.

Results:

<u>Dose</u> <u>(mg/kg/day)</u>	<u>No. of</u> <u>Doses</u>	<u>Mortality</u>	<u>Clinical Signs</u>
4,470	10	0/10	<u>First Week:</u> Lacrimation, stained perineal area, stained around eyes, nose and mouth and weight loss. <u>Second Week:</u> Salivation, stained perineal area and mouth, alopecia and weight loss. <u>Recovery Period:</u> None

Pathologic Changes:**

See Appendix [REDACTED]

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Summary: [REDACTED] was administered orally to young adult ChR-CD male rats at a repeated dose level of 4,470 mg/kg/day for ten days over a two-week period. Compound-related effects were noted in the liver, spleen, bone marrow and thymus. The histological effects of the test material on the spleen, sternal bone marrow and thymus are considered reversible since they were not observed after the 14-day recovery period, however, liver hypertrophy was still apparent.

* Composition: [REDACTED]

Report by:

O. Louis Dashiell
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Toxicologist

Approved by:

A. Michael Kaplan
A. Michael Kaplan
Chief, Acute Investigations Section

OLD/aph
[REDACTED]

Report No. 718-78

Date Issued: December 1, 1978

[REDACTED]
[REDACTED]
H-12,400 [REDACTED] - Chemicals, Dyes and Pigments Department

Oral Subacute - ChR-CD Rats

October 18, 1978

Results and Comments:

Gross and/or microscopic compound-related changes were observed in the liver, spleen, sternal bone marrow and thymus of male ChR-CD rats that received ten oral doses of [REDACTED] at 4470 mg/kg/dose.

Rats killed on the last day of the dosing period had a mean weight loss of 8% compared to a mean weight gain of 32% for the control group. Mean absolute weights of spleen, thymus, kidney and testis were all lower than controls; however, only spleen and thymus were lower than controls if calculated as a percentage of total body weight. Despite the overall decreased size of the test animals the mean absolute liver weight of the test group was increased 14%, corresponding to a 64% increase over controls when calculated as a percentage of total body weight.

On microscopic examination, the spleen, thymus and sternal bone marrow were slightly to markedly hypocellular (Table 1). Hypocellularity in the spleen was due primarily to the absence of the extramedullary hemopoiesis that is normally seen in young male rats. The more primitive members of the erythroid and granulocytic series were reduced in the sternal bone marrow with a corresponding increased fat content. The cortex of the thymus appeared to be more affected than the medullary regions. There was no apparent necrosis of hemopoietic or lymphoid cells suggesting that the hypocellularity may have

been due in part to the failure of the test animals to gain weight normally. The parenchymal cells of the liver were slightly enlarged and the cytoplasm lacked the cleared areas seen in controls which are associated with glycogen stores.

Most of the gross and microscopic changes described above were not observed in test animals killed after a 14-day recovery period. All of the animals had gained weight; the mean body weight of the test group was only 16% lower than control. The mean absolute and relative liver weight, however, remained increased over control (18% and 40% respectively).

Microscopic changes reflected the improved condition of the recovery test animals. Thymus and sternal bone marrow were histologically indistinguishable from controls. While the spleen differed in that the test animals exhibited more erythropoietic activity. Three of five livers, however, still showed evidence of decreased glycogen content. In three of five livers, there were also scattered degenerating hepatocytes.

One rat in this group exhibited an increased number of degenerating spermatocytes in the epididymis as well as degenerating germ cells sparsely scattered throughout the testis. The changes were unilateral. There was a small area of tubular atrophy in one testicle in a second rat in this group. These changes are possibly but not clearly compound related.

Other histologic changes noted in the trachea, lungs, liver, kidney, and thyroid are believed to be incidental or the result of intercurrent disease and are not effects of exposure to Zonyl FSN.

Representative sections from brain (9/10), adrenals, heart, eyes, upper and lower gastrointestinal tracts, pancreas (7/10), lymph nodes (8/10), and parathyroid (5/10) were unremarkable.

In summary, administration of [REDACTED] to male Chr-CD rats for ten days at 4470 mg/kg/dose results in weight loss, hypertrophy of the liver and hypocellularity of the spleen, bone marrow and thymus. The histological effects of the test compound on the spleen, sternal bone marrow and thymus are considered reversible since they were not observed after a 14-day recovery period. Liver hypertrophy, however, was still apparent. The significance of the low incidence of testicular changes is unclear.

Liver, spleen, kidney, testis and thymus were weighed.

Report by: _____

Nancy C. Chromey
Nancy C. Chromey, Ph.D.
Research Pathologist

Approved by: _____

William C. Krauss
William C. Krauss, D.V.M.
Chief, Pathology Section

NCC:WCK:mjb

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TABLE 1

MICROSCOPIC OBSERVATIONS OF TISSUES FROM CHR-CD RATS THAT
RECEIVED TEN ORAL DOSES OF [REDACTED]

	Compound	CONTROL											4470 mg/kg									
	Dose	0											0									
	Recovery Days	0											14									
Tissue/Lesion	Animal No.	237-	129	145	166	196	211	158	209	213	226	242	139	160	188	195	199	205	208	230	244	248
Spleen: Erythropoietic foci			1	1	±	±	1	-	-	±	±	-	-	-	-	-	-	2	1	1	2	1
Erythropoietic foci decreased			-	-	-	-	-	-	-	-	-	-	3	3	1	3	3	-	-	-	-	-
Sternal Bone Marrow: Hypocellular			-	-	-	-	-	-	-	-	-	-	2	3	2	1	0	-	-	-	-	-
Epididymis: Increased degenerating spermatocytes			-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1a	-	-	-	-
Testis: Scattered degenerating spermatocytes			-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1a	-	-	-	-
Focal tubular atrophy			-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1a	-	-	-
Thymus: Hypocellular			-	-	-	-	-	-	-	0	-	-	0	2	1	-	2	-	-	-	-	-
Lymph Nodes:			-	-	0	-	-	-	-	-	-	-	-	-	0	-	-	-	0	-	-	-
Trachea: Dilated glands			-	-	±	-	±	-	-	-	-	-	-	-	-	-	-	-	±	-	-	-
Lung: Interstitial pneumonitis			±	±	-	±	1	1	1	1	-	1	-	1	±	1	-	1	±	1	1	1
Focal consolidation			-	-	-	-	±	1	±	±	-	1	-	-	-	-	-	-	±	-	-	±
Perivascular cuffing			-	-	-	-	1	1	±	±	±	1	±	-	-	-	-	1	±	±	±	±
Peribronchiolar inflammatory cell infiltrate			-	-	-	-	-	-	-	-	-	±	-	-	-	-	-	-	-	-	-	-
Focal hemorrhage			-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-
Liver: Perinuclear cytoplasmic clearing			1	1	2	1	2	2	1	1	1	1	-	-	-	-	-	-	-	±	1	-
Lymphoreticular foci			-	±	-	±	±	-	1	-	±	±	-	-	-	-	-	±	-	-	±	±
Focal necrosis			-	±	-	-	-	-	±	-	-	-	-	-	-	-	-	-	-	-	-	±
Decreased glycogen			-	-	-	-	-	-	-	-	-	-	2	2	2	2	2	±	±	-	-	±
Cellular hypertrophy			-	-	-	-	-	-	-	-	-	-	±	±	±	±	±	-	-	-	-	-
Scattered hepatocyte degeneration			-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	±	-	±	-	±
Code: - = Lesion absent, tissue within normal histological limits ± = Isolated lesion; very slight change 1 = Slight change 2 = Moderate change																						
3 = Marked change a = unilateral 0 = Tissue missing																						

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PART II

H-12,400

TABLE 1 (Continued)

MICROSCOPIC OBSERVATIONS OF TISSUES FROM CHR-CD RATS THAT
RECEIVED TEN ORAL DOSES OF [REDACTED]

Compound		CONTROL												4470 mg/kg											
Dose		0												0											
Recovery Days		0						14						0						14					
Tissue/Lesion	Animal No.	237-	129	145	166	196	211	158	209	213	226	242	139	160	188	195	199	203	208	230	244	248			
Kidney: Focal tubular fibrosis			-	-	1	-	-	-	1	-	-		-	-	-	-	-	-	-	1	-	-			
Focal interstitial inflammatory infiltrate			-	-	1	-	-	-	-	-	-		-	-	-	-	-	-	-	1	-	-			
Hydronephrosis - right			-	-	-	-	1	-	1	-	-		-	1	-	-	1	-	-	1	-	-			
Cyst			-	-	-	-	-	-	1	-	1		-	1	-	-	1	-	-	1	-	-			

Code: - = Lesion absent, tissue within normal histological limits
 ± = Isolated lesion; very slight change
 1 = Slight change
 2 = Moderate change
 3 = Marked change
 u = Unilateral
 0 = Tissue missing

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