



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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Subject: Diflubenzuron 37100-8: Review of the Lifetime Oncogenic Study of
Diflubenzuron in Rats and Request for Removing Some Precautionary
Label Statements
Accession Nos. 252928, 252929, 252930, and 252931
Caswell No. 346A

To: Timothy Gardener, PM #17
Registration Division (TS-767)

Thru: Robert B. Jaeger, Section Head
Review Section #1
Toxicology Branch/HED (TS-769)

From: John H.S. Chen, D.V.M.
Review Section #1
Toxicology Branch/HED (TS-769)

Recommendation:

1. The registrant should be apprised of the deficiencies in the lifetime oncogenicity study of Diflubenzuron in rats, Hazleton Laboratories America Inc., Project No. 553-122, April 6, 1984.
2. The subject labeling should not be deleted until all the toxicity data requested in 1979 have been received and reviewed.

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Review and Assessment
(Hazleton Laboratories America Inc.)
104-Week Final Report

Procedure:

The procedures used in the 104-week oncology study of Diflubenzuron in rats are identical to those described previously in the 52-week interim report (Hazleton Laboratories America Inc., Project No. 553-122, October 15, 1982).

Results:

1. Mortality

<u>Dose Group (ppm)</u>	<u>No. of Animals (Dead/tested)</u>	
	<u>Males</u>	<u>Females</u>
0	34/100	48(1)/100
156	28/50*	24/50
625	17/50	15(1)/50
2500	21(1)/50	27/50
10000	21/50	26/50

* Significant difference from control.

Summary of Findings: Although a significant increase in the incidence of mortality was observed in the treated male group receiving 156 ppm Dimilin, the increase was not considered to be treatment-related. (The numbers in parentheses represent accidental deaths.)

2. Body Weights

<u>Dose Group (ppm)</u>	<u>Mean Weekly Body Weights (Weeks)</u>				
	<u>1</u>	<u>26</u>	<u>52</u>	<u>78</u>	<u>104</u>
<u>(Males)</u>					
0	271.0	565.6	617.2	608.6	557.8
156	270.7	567.1	619.8	606.5	534.4
625	267.6	552.9	607.2	606.0	548.4
2500	262.9	549.5	601.5	602.9	550.7
10000	266.9	550.9	608.0	597.5	528.6
<u>(Females)</u>					
0	181.4	309.9	352.1	388.0	402.9
156	179.0	301.8	340.1	381.9	364.8
625	178.2	297.2	342.3	385.7	371.2
2500	178.7	291.6	331.3	367.8	344.0
10000	175.6	288.8	328.5	359.3	357.6

Summary of Findings: There were no significant differences in the mean body weight values between the treated and control group (both sexes) during the study. However, a noticeable decrease in the mean body weight value for all male groups from week 92 to the week of termination (104 weeks) was noted. This decrease in the mean weekly body weights are likely due to the effect of geriatric change in the animals and are not related to the treatment of Dimilin.

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3. Food Consumption

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Dose Group (ppm) (Males)	Mean Weekly Food Consumption Values (Weeks)				
	1	26	52	78	104
0	164.0	166.0	175.0	181.0	175.2
156	172.2	172.8	169.4	182.3	165.0
625	169.1	167.6	167.9	181.3	168.7
2500	162.4	171.3	169.5	182.6	165.5
10000	166.2	173.5	173.5	178.6	88.0
(Females)					
0	136.6	124.5	133.7	136.6	150.7
156	132.7	119.1	126.4	156.4	128.0
625	138.4	122.7	130.9	155.2	135.7
2500	125.0	124.8	125.2	149.7	91.2
10000	152.3	128.8	130.9	150.1	147.5

Summary of Findings: No significant difference in the mean weekly food consumption values were observed between control and treated groups (both sexes) during the study. However, lower food consumption values were noted in the male group treated with 1000 ppm and the female group treated with 2500 ppm Dimilin at the 104-week. These decreases are not considered to be treatment-related.

4. Clinical Examinations

Observations	Incidence Summary of Clinical Signs*									
	Males (ppm)					Females (ppm)				
	0	156	625	2500	10000	0	156	625	2500	10000
Hunched	55	27	26	16	22	56	22	20	29	25
Thin	52	25	25	18	24	59	23	23	29	26
Languid	11	11	9	7	11	26	8	15	15	15
Soft feces	57	21	21	9	13	27	16	10	8	13
Rhinorrhea	66	38	35	27	41	67	31	29	30	28
Urine stains	39	25	20	16	24	44	20	18	20	21
Alopecia	48	17	18	14	15	46	20	28	19	24
Rough hair-coat	72	35	29	23	33	63	30	29	32	35
Sores	71	35	35	28	37	21	16	11	11	12
Blood crust(eye)	42	29	20	13	20	60	27	31	30	21
Squinting	14	10	5	4	6	14	8	10	4	3
Lacrimation	32	22	13	9	11	32	14	13	14	16
Chromodacryorrhea	45	42	43	83	29	37.5	95	52	83	83
Swollen neck	14	14	8	11	11	11	2	1	1	3

Summary of Findings: The most common clinical-signs found in control and treated animals were hunched and/or thin appearance, urine stains, alopecia, and rough hair-coat. The symptoms of swollen necks, lacrimation, rhinorrhea, and blood crust on eye or eyelids which were associated with Sialodacryoadenitis caused by the presence of sendai virus have been confirmed. The viral infection had no apparent lasting effect on the general health of the animals. There were no treatment-related effects on the incidence of clinical signs which can be observed during the study.

(* Numerals indicate the no. of animals exhibiting a particular finding at least once during the study)

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5. Hematology

(a) Mean Clinical Hematology Values of Male Rats at Week 104

Dose (ppm)	0	156	625	2500	10000
* HCT (%)	40.5	42.0	41.8	40.1	48.9*
* HGB (g/dl)	14.0	14.7	13.9	13.5	16.7*
* RBC (Th/ul)	7.3	7.6	7.1	6.8	8.5*
WBC (Th/ul)	8.9	10.5	9.4	10.4	9.7
MCV (fl)	56.0	55.4	59.2	59.0	57.2
MCH (Pg)	19.4	19.4	19.7	19.9	19.6
MCHC (%)	34.7	35.1	33.3	33.7	34.2
* Metheme (g/dl)	0.11	0.16*	0.18*	0.25*	0.3*
* Sulfheme (g/dl)	0.015	0.034*	0.079*	0.121*	0.063*
Platelet (Th/ul)	1211	1159	1153	1096	1227
RETIC (%RBC)	2.2	1.7	2.0	2.8	1.3
* M/E Ratio	2.45	1.62*	1.76*	1.47*	1.53*

* Significant changes; HCT - Hematocrit; HGB - Hemoglobin; RBC - Red Blood Cell; WBC - White Blood Cell; MCH - Mean Corpuscular hemoglobin; Metheme - Methemoglobin; Sulfheme - Sulfhemoglobin; RETIC - Reticulocytes Count; MCHC - Mean Corpuscular Hemoglobin Conc.; M/E Ratio - Myeloid/Erythroid Ratio.

Summary of Findings for Male Rats: Significant decreases in the mean hematocrit values were observed in the 10000 ppm level group at week 52, but the HCT values were significantly increased in the same level group at week 104. The mean hemoglobin and erythrocyte counts were also significantly decreased for the 625, and 10000 ppm level group at week 52, but a significantly increased hemoglobin and a moderately increased erythroid count were observed in the 10000 ppm level group at week 104. The mean corpuscular hemoglobin value (MCH) and reticulocyte counts (RETIC) were significantly increased in the 10000 ppm level group at week 52, and a similar trend of increase in the MCH values was also noted in the 625 and 2500 ppm level groups at week 104. The absolute values of methemoglobin and sulfhemoglobin demonstrated a treatment-related increase in the Dimilin treated groups (from 156 through 10000 ppm) at week 104. The myeloid:erythroid (M:E) ratios were decreased in all treated groups at week 104. Such changes in the peripheral blood may contribute to the cause of erythroid hyperplasia of the bone marrow.

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5. Hematology - Continued

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(b) Mean Clinical Hematology Values of Female Rats at Week 104

Dose (ppm)	0	156	625	2500	10000
HCT (%)	42.1	43.5	43.0	40.1	40.7
HGB (g/dl)	14.0	14.3	14.4	13.6	13.5
RBC (Th/ul)	7.0	7.3	6.9	6.4	6.1
WBC (Th/ul)	7.4	7.0	8.1	8.0	7.7
* MCV (fl)	60.6	59.5	61.9	62.4*	66.9*
MCH (Pg)	20.2	19.7	20.8	21.3	22.3
MCHC (%)	33.4	33.1	33.5	34.0	33.3
* Metheme. (g/dl)	0.104	0.188*	0.225*	0.295*	0.309*
* Sulfheme (g/dl)	0.024	0.044*	0.084*	0.146*	0.145*
Platelet (Th/ul)	967	955	945	1147	973
* RETIC (%RBC)	2.7	2.8	3.3	4.5*	6.9*
* M/E Ratio	1.93	1.09*	1.34*	1.29*	1.05*

* Significant changes;

Summary of Findings for Female Rats: The mean hematocrit values for the 10000 ppm level group were significantly lower than that of the control group at week 52. However, the HCT values for the 10000 ppm value at week 104 were not significantly different from control value at week 104. The mean hemoglobin and erythrocyte counts were significantly decreased in the 2500 and 10000 ppm level groups at week 52. But, only a moderate decrease in these values was observed in the same treated group at week 104. Significant increases in the mean corpuscular hemoglobin value and reticulocytes count were also noted in the 2500 and 10000 ppm level groups at week 104. The absolute values of methemoglobin and sulfhemoglobin were found in a compound-related increase in all treated groups at week 104. The myeloid:erythroid ratios were also decreased in all treated groups at week 104.

(c) Methemoglobin and Sulfhemoglobin Values at the Week 52 and 104 (Value=g/dl)

Dose (ppm)	0	156	625	2510	10000
<u>Males</u>					
Metheme (52 Week)	0.04	0.31	0.22	0.37 ¹	0.38
" (104 ")	0.11	0.16	0.18	0.25	0.30
Sulfheme (52 Week)	0.02	0.21	0.14	0.11	0.16
" (104 ")	0.015	0.034	0.019	0.121	0.063
<u>Females</u>					
Metheme (52 Week)	0.10	0.10	0.20	0.30	0.30
" (104 ")	0.104	0.188	0.225	0.295	0.309
Sulfheme (52 Week)	0.02	0.03	0.14	0.02	0.05
" (104 ")	0.024	0.044	0.084	0.146	0.145

6. Serology Screening

The presence of Sendai virus and sialodacryoadenitis was detected in 12 of 12 serum samples tested.

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7. Gross Pathology(a) Incidence Summary of Gross Pathology Findings for Animals Dying Prior to Study Termination

Dose (ppm)	Males (ppm)					Females (ppm)				
	0	156	625	2500	10000	0	156	625	2500	10000
No. Examined	34	28	17	22	21	49	24	16	27	26
No. Not Remarkable:										
* Brain	19	14	10	13	15	18	6	8	10	7
* Pituitary	20	13	8	9	12	8	4	1	6	0
* Adrenals	25	22	13	17	17	22	9	5	8	15
Thyroid	33	26	17	19	20	49	24	16	26	26
Esophagus	34	28	17	22	21	49	23	16	26	26
Trachea	34	28	17	22	21	49	24	16	27	26
* Lung W/Bronchi	14	14	8	9	11	28	17	13	14	17
Heart	27	25	14	16	19	44	19	14	21	21
Spleen	24	26	12	19	14	39	20	14	23	21
* Liver	18	14	11	16	9	30	17	8	18	19
Kidneys	17	19	11	13	12	36	12	11	15	16
Ureter	33	28	17	21	21	48	22	16	26	24
Stomach	17	10	6	11	10	22	11	6	7	11
Duodenum	32	27	16	21	21	48	22	16	27	24
Jejunum	32	25	16	21	21	47	20	16	22	24
Ileum	33	27	16	21	19	47	22	16	24	24
Pancreas	33	27	14	22	19	49	23	15	26	25
Cecum	30	23	10	19	16	44	19	15	24	22
Colon	33	27	16	21	21	46	24	16	27	24
Rectum	33	27	16	22	21	46	24	16	27	24
Testes W/Epidid	25	23	9	17	14	-	-	-	-	-
Prostate	32	26	17	20	18	-	-	-	-	-
Urinary Bladder	30	28	16	20	17	49	22	16	24	24
Ovaries	-	-	-	-	-	49	24	16	27	26
Uterus	-	-	-	-	-	49	24	16	27	26
Cervix	-	-	-	-	-	48	22	16	27	26
Thymus	32	26	15	22	20	49	24	16	27	26
Eye	26	26	16	18	18	41	21	14	24	23
Optic Nerve	34	28	17	22	21	49	24	16	27	26
Skeletal Muscle	34	28	17	22	20	49	24	16	27	25
Skin	29	24	15	20	17	43	23	14	27	25
Mammary Gland	33	28	17	22	21	38	17	10	20	22
Sternum W/Marrow	34	27	17	22	21	49	24	16	27	25
Nasal Pass/Cavit	34	28	16	22	21	49	24	15	26	26
Tongue	34	28	17	22	21	49	24	16	26	26
Oral Cavity	32	28	16	21	19	47	23	16	25	26
Seminal Vesicle	24	24	15	22	15	-	-	-	-	-
Lymph-Node	27	19	7	17	11	32	15	12	15	21
Thoracic Cavity	31	26	16	20	20	49	24	16	27	24
Peritoneal Cavity	30	24	14	22	16	44	22	15	26	24
Subcutaneous Tissue	28	25	16	21	18	31	14	8	14	20
Head Coronal	31	28	16	22	18	47	24	16	27	26
Diaphragm	33	28	17	22	19	49	23	15	27	25
Bone	33	28	14	22	19	48	24	16	26	26
Organ	27	23	12	17	19	43	20	14	25	17

* Noticeable changes

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Summary of Findings: There were increased incidences of indented brains and enlarged pituitaries in animals of both sexes treated with Dimilin. Whether, this to be attributed to the age-related changes in this strain of rat is not clear. Although no dose-related effect was indicated, the noticeable frequency of dark and/or speckled adrenals and the increased incidence of mottled and/or pale focus in the livers of treated animals of both sexes were also observed. No other pathological findings were found to be remarkable.

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7. Gross Pathology (Continued)

(b) Incidence Summary of Gross Pathology Findings for Animals Sacrificed at Study Termination.

Dose (ppm)	Males					Females				
	0	156	625	2500	10000	0	156	625	2500	10000
No. Examined	66	22	33	28	29	54	26	34	23	24
No. Not Remarkable:										
* Brain	62	20	31	25	26	30	8	20	13	13
* Pituitary	34	15	14	18	15	5	1	6	3	2
* Adrenals	27	15	24	21	18	4	4	12	5	5
Thyroid	62	21	30	24	26	49	26	33	21	23
Parathyroid	59	22	32	27	29	50	26	34	22	23
Esophagus	66	22	33	28	29	51	26	34	23	24
Trachea	66	22	33	28	29	51	26	34	23	24
* Lung W/Bronchi	57	21	25	24	24	47	24	29	17	20
Heart	63	21	32	28	28	51	26	34	23	24
* Spleen	58	20	26	19	21	46	20	31	17	19
Liver	18	8	13	13	10	19	11	13	8	4
* Kidneys	47	14	15	19	19	33	16	21	11	15
Pancreas	59	21	31	28	27	47	26	33	21	24
Colon	65	22	33	28	29	51	26	34	23	24
Mesenteric LN	63	21	25	28	28	47	25	31	23	24
Testes W/Epidid	48	16	26	19	19	-	-	-	-	-
Duodenum	66	22	32	28	29	51	26	34	23	24
Jejunum	66	22	30	28	29	51	25	34	23	24
Ileum	66	22	33	28	29	50	26	34	23	24
Prostate	61	21	32	27	28	-	-	-	-	-
Urinary Bladder	66	22	33	27	29	49	26	34	22	23
Ovaries	-	-	-	-	-	41	18	25	15	17
Uterus	-	-	-	-	-	38	18	22	15	17
Cervix	-	-	-	-	-	44	25	33	22	23
Thymus	66	22	33	28	29	51	26	34	23	24
Eye	61	21	32	27	23	51	26	34	21	24
Optic Nerves	66	22	33	28	29	51	26	34	23	24
Harderian GL	66	22	33	28	29	51	26	34	22	24
Skeletal Muscle	65	22	33	28	29	51	26	34	23	24
Skin	56	19	23	26	19	49	23	32	23	23
Mammary Gland	61	20	33	27	27	26	12	22	11	14
Sternum W/Marrow	66	22	33	28	29	51	26	34	23	24
Nasal Pass/Cavit	66	22	33	28	29	51	26	34	23	24
Nasopharynx	66	22	33	28	29	51	26	34	23	24
Paranasal Sinus	66	22	33	28	29	51	26	34	23	24
Tongue	66	22	33	28	29	51	26	34	23	24
Oral Cavity	66	22	33	28	29	51	26	34	23	24
Seminal Vesicle	60	22	31	27	25	-	-	-	-	-
Lymph-Node	39	16	25	21	22	43	16	29	19	17
Thoracic Cavity	65	22	33	28	28	51	26	32	23	24
Peritoneal Cavity	64	22	30	28	28	50	26	33	22	23
Subcutaneous Tissue	61	20	33	22	26	26	14	26	9	16
Head, Coronal	66	22	33	27	29	51	26	34	23	24
Diaphragm	66	22	33	28	29	51	26	34	23	24
Mesentary	66	22	33	28	29	51	26	34	23	24
Vagina	-	-	-	-	-	50	26	34	23	24
Penis	65	22	32	28	29	-	-	-	-	-

* Noticeable changes

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Summary of Findings: Increased incidences of indented brains and enlarged pituitaries were also observed in animals of both sexes treated with Dimilin at terminal sacrifice. Although no dose-related effect was noted, the noticeable frequency of dark and/or speckled adrenals and the increased incidences of enlarged spleen were observed. Slight increase in the observation of granular materials in kidneys was also noted in the treated animals of both sexes. No other pathological findings were found to be remarkable at terminal sacrifices.

8. Organ Weights

There was a statistically significant increase in both absolute and relative spleen weights in animals of both sexes treated with 2500 and 10000 ppm Dimilin at terminal sacrifice. Such an increase was correlated well with the increased incidence of enlarged spleen in the same dose-treated female and male groups. Significant increases in the liver weight of female groups treated with 2500 and 10000 ppm and significant decrease in the terminal body weight of females treated with 10000 ppm Dimilin were observed in this study.

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9. Individual Histopathological Findings to the Neoplastic Lesions for
Animals Found Dead or Sacrificed in Extremis During the Weeks 1-104.

Dose Levels (ppm)	Males						Females					
	H	0	156	625	2500	10000	H	0	156	625	2500	10000
<u>Pituitary</u>												
Carcinoma (D)	15	12	9	6	8	4	45	18	6	8	8	11
	300	34	28	17	22	21	287	47	24	16	27	26
Carcinoma (T)	15	15	1	3	2	5	45	13	15	11	11	11
	300	65	22	33	28	29	297	51	26	34	23	24
Adenoma (D)	117	1	7	3	3	3	188	17	13	6	9	11
	300	34	28	17	22	21	287	47	24	16	27	26
Adenoma (T)	117	17	10	11	11	11	188	33	9	18	9	10
	300	65	22	33	28	29	287	51	26	34	23	24
<u>Adrenals</u>												
Pheochromocytoma (D)	0	0	0	1	0	0	0	1	0	0	0	0
	33	27	17	22	21	21	48	23	16	26	26	26
Pheochromocytoma (T)	9	4	2	3	6	6	3	0	0	0	1	1
	66	22	33	28	29	29	51	26	34	23	24	24
<u>Thyroid</u>												
Follicular Cell	6	2	3	0	0	0	3	2	2	1	0	0
	291	33	28	16	22	20	272	49	23	16	27	26
Adenoma (D)	6	4	2	3	2	4	3	0	1	1	2	1
	291	66	22	33	28	29	272	51	26	34	23	24
Follicular Cell	2	1	1	0	1	1	1	0	0	0	1	0
	291	33	28	16	22	20	272	39	23	16	17	26
Carcinoma (D)	2	0	0	0	2	1	1	1	0	0	0	0
	291	66	22	33	28	28	272	51	26	34	23	24
Follicular Cell	0	0	0	0	0	0	1	0	0	0	0	1
	33	28	16	22	20	20	48	23	16	27	26	26
"C" Cell Adenoma (D)	4	1	0	0	1	1	0	0	1	0	1	1
	66	22	33	28	29	29	51	26	34	23	24	24
"C" Cell Adenoma (T)	17	1	1	1	0	1	11	3	0	0	0	1
	291	33	28	16	22	20	272	48	23	16	27	26
"C" Cell Carcinoma (D)	17	3	2	2	3	4	11	11	1	5	4	3
	291	66	22	33	28	29	272	51	26	34	23	24
<u>Liver</u>												
Neoplastic Nodule (D)	21	2	1	0	0	0	36	0	0	1	1	1
	290	34	28	17	22	21	274	49	24	16	27	26
Neoplastic Nodule (T)	21	6	0	2	2	7	36	4	2	8	1	1
	290	66	22	33	28	29	274	51	26	34	23	24
Hepatocellular Carcinoma (D)	15	2	1	0	0	0	6	0	0	0	0	0
	318	34	28	17	22	21	295	49	24	16	27	26
Hepatocellular Carcinoma (T)	15	3	0	2	1	1	6	0	2	0	1	1
	318	66	22	33	28	29	295	54	26	34	23	24
<u>Testes</u>												
Interstitial Cell	30	3	2	0	2	2	0	0	0	0	0	0
	298	34	28	17	22	21	0	0	0	0	0	0
Tumor-Unilateral (D)	30	7	3	4	3	2	0	0	0	0	0	0
	298	66	22	34	28	29	0	0	0	0	0	0
Interstitial Cell	30	7	3	4	3	2	0	0	0	0	0	0
	298	66	22	34	28	29	0	0	0	0	0	0
Tumor-Unilateral (T)	30	7	3	4	3	2	0	0	0	0	0	0
	298	66	22	34	28	29	0	0	0	0	0	0
<u>Uterus</u>												
Endometrial Stromal Polyp	0	0	0	0	0	0	30	0	0	0	2	1
	0	0	0	0	0	0	243	47	24	16	25	26
(D)	0	0	0	0	0	0	30	9	3	4	3	3
	0	0	0	0	0	0	243	51	26	34	23	24
Endometrial Stromal Polyp	0	0	0	0	0	0	30	9	3	4	3	3
	0	0	0	0	0	0	243	51	26	34	23	24
(T)	0	0	0	0	0	0	243	51	26	34	23	24

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9. Histopathological Findings to the Neoplastic Lesions - Continued

Dose Levels (ppm)	Males						Females					
	H	0	156	625	2500	10000	H	0	156	625	2500	10000
<u>Uterus</u>												
Endometrial Stromal Polyp (D)	0	0	0	0	0	0	30	0	0	0	2	1
	0	0	0	0	0	0	243	47	24	16	25	26
Endometrial Stromal Polyp (T)	0	0	0	0	0	0	30	9	3	4	3	3
	0	0	0	0	0	0	243	51	26	34	23	24
Squamous Cell Carcinoma (D)	0	0	0	0	0	0	0	0	0	0	0	1
	0	0	0	0	0	0	47	24	16	25	26	
Squamous Cell Carcinoma (T)	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	51	26	34	23	24	
<u>Spleen</u>												
Monocytic Leukemia (D)	0	0	0	0	1		0	0	0	0	0	0
	34	28	17	22	21		48	23	16	27	26	
Monocytic Leukemia (T)	0	0	0	0	0		0	0	0	0	0	0
	66	22	33	28	29		51	26	34	23	24	
Malignant Lymphoma, Histiocytic (D)	1	0	2	0	0		0	0	0	0	0	0
	34	28	17	22	21		48	23	16	27	26	
Malignant Lymphoma, Histiocytic (T)	0	0	2	0	0		0	0	0	0	0	0
	66	22	33	28	29		51	26	34	23	24	
<u>Thymus</u>												
Malignant Fibrous, Histiocytoma (D)	1	0	0	0	0		0	0	0	0	0	0
	23	23	15	16	15		41	20	14	19	19	
Malignant Fibrous, Histiocytoma (T)	0	0	0	0	0		0	0	0	0	0	0
	63	22	32	19	27		46	22	32	22	24	
<u>Mammary Gland</u>												
Adenocarcinoma (D)	0	1	0	0	0	0	49	6	7	3	2	1
	267	16	7	9	9	9	289	49	23	16	27	25
Adenocarcinoma (T)	0	0	0	0	0	0	49	8	5	2	6	1
	267	10	7	1	2	2	289	51	26	33	23	24
Fibroadenoma (D)	2	0	0	0	0	0	110	0	1	0	1	0
	267	16	7	9	9	9	286	49	23	16	27	25
Fibroadenoma (T)	2	0	0	0	0	0	110	14	6	6	5	5
	267	10	7	1	2	2	286	51	26	33	23	24
<u>Skin</u>												
Fibroma (D)	1	0	0	0	0	0	0	0	0	0	0	0
	34	26	17	22	21		49	24	15	27	25	
Fibroma (T)	2	1	0	0	1		0	0	0	0	0	0
	65	22	33	28	29		51	26	34	23	24	
Squamous Cell Papilloma (D)	1	0	0	0	1		0	0	0	0	0	0
	34	26	17	22	21		48	24	15	27	25	
Squamous Cell Papilloma (T)	1	1	0	2	2		0	0	0	0	0	0
	65	22	33	28	29		51	26	34	23	24	
Fibrosarcoma (D)	0	0	0	0	0	0	1	0	0	0	0	0
	192	34	26	17	22	21	177	24	15	27	25	
Fibrosarcoma (T)	0	0	1	2	0	0	1	0	0	0	0	0
	192	65	22	33	28	29	177	51	26	34	23	24

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9. Histopathological Findings to the Neoplastic Lesion - Continued

Dose Levels (ppm)	Males						Females					
	H	0	156	625	2500	10000	H	0	156	625	2500	10000
Squamous Cell Carcinoma (D)		0	0	0	0	0		1	0	0	0	0
		34	26	17	22	21		49	24	15	27	25
Squamous Cell Carcinoma (T)		0	0	0	0	0		0	0	0	0	0
		65	22	33	28	29		51	26	34	23	24
Keratoacanthoma (D)	4	3	2	1	1	1	1	1	0	0	1	0
	103	34	26	17	22	21	91	49	24	15	27	25
Keratoacanthoma (D)	4	6	1	5	6	7	1	0	1	0	0	0
	103	65	22	33	28	29	91	51	26	34	23	24

* Noticeable increase of incidence rate (%); (D)-Animals found in unscheduled deaths;
 (T) - Animals sacrificed at terminal sacrifices; H - Historical Control Data.

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SACRIFICED IN EXTREMIS DURING THE WEEK 1- 104

Dose Levels (ppm)	Males					Females				
	0	156	625	2500	10000	0	156	625	2500	10000
<u>Brain</u>										
Ventral Compression (T)	<u>3</u> 66	<u>1</u> 22	<u>1</u> 33	<u>2</u> 28	<u>3</u> 29	<u>16</u> 51	<u>15</u> 26	<u>16</u> 34	<u>9</u> 23	<u>9</u> 24
Ventral Compression (D)	<u>11</u> 34	<u>6</u> 26	<u>5</u> 17	<u>7</u> 22	<u>4</u> 21	<u>25</u> 49	<u>12</u> 24	<u>8</u> 16	<u>14</u> 27	<u>16</u> 26
<u>Pituitary</u>										
Focal Hyperplasia (D)	<u>4</u> 34	<u>1</u> 28	<u>0</u> 17	<u>1</u> 22	<u>1</u> 21	<u>2</u> 47	<u>0</u> 24	<u>1</u> 16	<u>5</u> 27	<u>1</u> 26
Focal Hyperplasia (T)	<u>17</u> 65	<u>5</u> 22	<u>5</u> 33	<u>7</u> 28	<u>2</u> 29	<u>2</u> 51	<u>1</u> 26	<u>4</u> 34	<u>2</u> 23	<u>1</u> 24
<u>Adrenals</u>										
Congestions (D)	<u>5</u> 33	<u>7</u> 27	<u>6</u> 17	<u>8</u> 22	<u>3</u> 21	<u>20</u> 48	<u>12</u> 23	<u>7</u> 16	<u>10</u> 26	<u>10</u> 26
Congestions (T)	<u>0</u> 66	<u>0</u> 22	<u>1</u> 33	<u>1</u> 28	<u>1</u> 29	<u>26</u> 51	<u>18</u> 26	<u>19</u> 34	<u>8</u> 23	<u>12</u> 24
Angiectasis (D)	<u>2</u> 33	<u>2</u> 27	<u>1</u> 17	<u>2</u> 22	<u>4</u> 21	<u>31</u> 48	<u>18</u> 23	<u>11</u> 16	<u>17</u> 26	<u>19</u> 26
Angiectasis (T)	<u>7</u> 66	<u>5</u> 22	<u>4</u> 33	<u>5</u> 28	<u>0</u> 29	<u>43</u> 51	<u>19</u> 26	<u>23</u> 34	<u>19</u> 23	<u>21</u> 24
<u>Thyroid</u>										
"C" Cell Hyperplasia (D)	<u>3</u> 33	<u>2</u> 28	<u>1</u> 16	<u>2</u> 22	<u>0</u> 20	<u>2</u> 48	<u>1</u> 23	<u>0</u> 16	<u>0</u> 27	<u>3</u> 26
"C" Cell Hyperplasia (T)	<u>8</u> 66	<u>1</u> 22	<u>3</u> 33	<u>4</u> 28	<u>3</u> 29	<u>4</u> 51	<u>3</u> 26	<u>1</u> 34	<u>2</u> 23	<u>4</u> 24
Follicular Ectasia (D)	<u>8</u> 33	<u>5</u> 28	<u>4</u> 16	<u>3</u> 22	<u>1</u> 20	<u>4</u> 48	<u>2</u> 23	<u>2</u> 16	<u>2</u> 27	<u>2</u> 26
Follicular Ectasia (T)	<u>12</u> 66	<u>4</u> 22	<u>6</u> 33	<u>1</u> 28	<u>6</u> 29	<u>3</u> 51	<u>2</u> 26	<u>4</u> 34	<u>2</u> 23	<u>4</u> 24
<u>Lung W/Branchi</u>										
Perivascular/Peribronchial Hyperplasia (D)	<u>24</u> 34	<u>23</u> 28	<u>15</u> 17	<u>20</u> 22	<u>14</u> 21	<u>36</u> 49	<u>18</u> 24	<u>15</u> 16	<u>14</u> 27	<u>20</u> 26
Perivascular/Peribronchial Hyperplasia (T)	<u>64</u> 66	<u>22</u> 22	<u>33</u> 33	<u>28</u> 28	<u>28</u> 29	<u>50</u> 51	<u>21</u> 26	<u>33</u> 34	<u>19</u> 23	<u>24</u> 24
Congestions (D)	<u>13</u> 34	<u>16</u> 28	<u>9</u> 17	<u>13</u> 22	<u>6</u> 21	<u>15</u> 49	<u>10</u> 24	<u>2</u> 16	<u>9</u> 27	<u>11</u> 26
Congestions (T)	<u>6</u> 66	<u>4</u> 22	<u>10</u> 33	<u>3</u> 28	<u>1</u> 29	<u>4</u> 51	<u>1</u> 26	<u>1</u> 34	<u>0</u> 23	<u>0</u> 24
Pneumonitis (D)	<u>10</u> 34	<u>9</u> 28	<u>4</u> 17	<u>8</u> 22	<u>7</u> 21	<u>10</u> 49	<u>9</u> 24	<u>4</u> 16	<u>9</u> 27	<u>9</u> 26
Pneumonitis (T)	<u>31</u> 66	<u>11</u> 22	<u>16</u> 33	<u>17</u> 28	<u>17</u> 29	<u>19</u> 51	<u>8</u> 26	<u>14</u> 34	<u>14</u> 23	<u>9</u> 24
<u>Heart</u>										
Degenerative Cardiomyopathy (D)	<u>19</u> 34	<u>18</u> 28	<u>8</u> 17	<u>15</u> 22	<u>10</u> 21	<u>21</u> 49	<u>12</u> 24	<u>7</u> 16	<u>10</u> 27	<u>9</u> 26
Degenerative Cardiomyopathy (T)	<u>0</u> 66	<u>0</u> 22	<u>0</u> 33	<u>0</u> 28	<u>0</u> 29	<u>0</u> 51	<u>0</u> 26	<u>0</u> 34	<u>0</u> 23	<u>0</u> 24
Thrombus (D)	<u>0</u> 19	<u>1*</u> 28	<u>3*</u> 17	<u>0</u> 22	<u>1*</u> 21	<u>0</u> 49	<u>1*</u> 24	<u>0</u> 16	<u>0</u> 10	<u>1*</u> 9

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10. Histopathological Findings to the Nonneoplastic Lesions - Continued

Dose Levels (ppm)	Males					Females				
	0	156	625	2500	10000	0	156	625	2500	10000
Thrombus (T)	$\frac{0}{66}$	$\frac{1}{22}$	$\frac{0}{33}$	$\frac{1}{28}$	$\frac{1}{29}$	$\frac{0}{51}$	$\frac{0}{26}$	$\frac{0}{34}$	$\frac{0}{23}$	$\frac{0}{24}$
<u>Spleen</u>										
Pigmented Macrophage, Increased (D)	$\frac{20}{34}$	$\frac{21^*}{28}$	$\frac{13^*}{17}$	$\frac{19^*}{22}$	$\frac{14^*}{21}$	$\frac{33}{48}$	$\frac{19^*}{23}$	$\frac{16^*}{16}$	$\frac{24^*}{27}$	$\frac{26^*}{26}$
Pigmented Macrophage, Increased (T)	$\frac{14}{66}$	$\frac{3}{22}$	$\frac{20^*}{33}$	$\frac{23^*}{28}$	$\frac{25^*}{29}$	$\frac{8}{51}$	$\frac{7^*}{26}$	$\frac{20^*}{34}$	$\frac{21^*}{23}$	$\frac{21^*}{24}$
Extramedullary Hematopoiesis (D)	$\frac{1}{20}$	$\frac{3}{28}$	$\frac{1}{17}$	$\frac{0}{22}$	$\frac{3}{21}$	$\frac{5}{49}$	$\frac{1}{24}$	$\frac{2}{16}$	$\frac{4}{27}$	$\frac{1}{26}$
Extramedullary Hematopoiesis (T)	$\frac{0}{66}$	$\frac{0}{22}$	$\frac{3}{33}$	$\frac{3}{28}$	$\frac{1}{29}$	$\frac{1}{51}$	$\frac{5}{26}$	$\frac{2}{34}$	$\frac{1}{23}$	$\frac{0}{24}$
Congestion/Hemorrhage (D)	$\frac{1}{34}$	$\frac{0}{28}$	$\frac{0}{17}$	$\frac{1}{22}$	$\frac{2}{21}$	$\frac{1}{48}$	$\frac{1}{23}$	$\frac{1}{16}$	$\frac{3}{27}$	$\frac{0}{26}$
Congestion/Hemorrhage (T)	$\frac{0}{66}$	$\frac{0}{22}$	$\frac{1^*}{33}$	$\frac{4^*}{28}$	$\frac{1^*}{29}$	$\frac{0}{51}$	$\frac{0}{26}$	$\frac{1^*}{34}$	$\frac{2^*}{23}$	$\frac{0}{24}$
<u>Liver</u>										
Non-Suppurative Pericholangitis (D)	$\frac{14}{34}$	$\frac{18}{28}$	$\frac{6}{17}$	$\frac{15}{22}$	$\frac{5}{21}$	$\frac{20}{49}$	$\frac{8}{24}$	$\frac{6}{16}$	$\frac{10}{27}$	$\frac{10}{26}$
Non-Suppurative Pericholangitis (T)	$\frac{53}{66}$	$\frac{17}{22}$	$\frac{30}{33}$	$\frac{23}{28}$	$\frac{22}{29}$	$\frac{36}{51}$	$\frac{19}{26}$	$\frac{23}{34}$	$\frac{19}{23}$	$\frac{17}{24}$
Hepatocytic Vacuolization (D)	$\frac{9}{34}$	$\frac{7}{28}$	$\frac{3}{17}$	$\frac{8}{22}$	$\frac{6}{21}$	$\frac{29}{49}$	$\frac{9}{24}$	$\frac{10}{16}$	$\frac{5}{27}$	$\frac{17}{26}$
Hepatocytic Vacuolization (T)	$\frac{22}{66}$	$\frac{6}{22}$	$\frac{13}{33}$	$\frac{12}{28}$	$\frac{13}{29}$	$\frac{44}{51}$	$\frac{13}{26}$	$\frac{19}{34}$	$\frac{15}{23}$	$\frac{21}{24}$
Bile Duct Hyperplasia (D)	$\frac{20}{34}$	$\frac{20}{28}$	$\frac{9}{17}$	$\frac{18}{22}$	$\frac{11}{21}$	$\frac{31}{49}$	$\frac{11}{24}$	$\frac{7}{16}$	$\frac{15}{27}$	$\frac{19}{26}$
Bile Duct Hyperplasia (T)	$\frac{59}{66}$	$\frac{18}{22}$	$\frac{30}{33}$	$\frac{24}{28}$	$\frac{26}{29}$	$\frac{37}{51}$	$\frac{23}{26}$	$\frac{25}{34}$	$\frac{21}{23}$	$\frac{20}{24}$
Pigmented Macrophage, Increased (D)	$\frac{8}{34}$	$\frac{7^*}{28}$	$\frac{7^*}{17}$	$\frac{19^*}{22}$	$\frac{12^*}{21}$	$\frac{18}{49}$	$\frac{12^*}{24}$	$\frac{14^*}{16}$	$\frac{19^*}{27}$	$\frac{22^*}{26}$
Pigmented Macrophage, Increased (T)	$\frac{14}{66}$	$\frac{3}{22}$	$\frac{20^*}{33}$	$\frac{23^*}{28}$	$\frac{25^*}{29}$	$\frac{8}{51}$	$\frac{7^*}{26}$	$\frac{20^*}{34}$	$\frac{21^*}{23}$	$\frac{21^*}{24}$
Focus/Area of Cell Alteration (D)	$\frac{4}{34}$	$\frac{3}{28}$	$\frac{1}{17}$	$\frac{9}{22}$	$\frac{5}{21}$	$\frac{8}{49}$	$\frac{5}{11}$	$\frac{8}{16}$	$\frac{6}{27}$	$\frac{2}{26}$
Focus/Area of Cell Alteration (T)	$\frac{46}{66}$	$\frac{14}{22}$	$\frac{26}{33}$	$\frac{24}{28}$	$\frac{26}{29}$	$\frac{22}{51}$	$\frac{10}{26}$	$\frac{18}{34}$	$\frac{14}{23}$	$\frac{12}{24}$
Extramedullary Hematopoiesis (D)	$\frac{2}{34}$	$\frac{0}{28}$	$\frac{0}{17}$	$\frac{1}{22}$	$\frac{1}{21}$	$\frac{7}{49}$	$\frac{3}{24}$	$\frac{2}{16}$	$\frac{2}{27}$	$\frac{1}{26}$
Extramedullary Hematopoiesis (T)	$\frac{7}{66}$	$\frac{1}{22}$	$\frac{2}{33}$	$\frac{6}{28}$	$\frac{4}{29}$	$\frac{5}{51}$	$\frac{6}{26}$	$\frac{4}{34}$	$\frac{4}{23}$	$\frac{3}{24}$
<u>Kidneys</u>										
Calculi/Microcalculi (D)	$\frac{15}{34}$	$\frac{19}{28}$	$\frac{11}{17}$	$\frac{12}{22}$	$\frac{10}{21}$	$\frac{42}{49}$	$\frac{22}{24}$	$\frac{15}{16}$	$\frac{23}{27}$	$\frac{21}{26}$
Calculi/Microcalculi (T)	$\frac{48}{66}$	$\frac{16}{22}$	$\frac{26}{33}$	$\frac{25}{28}$	$\frac{22}{29}$	$\frac{47}{51}$	$\frac{26}{26}$	$\frac{33}{34}$	$\frac{20}{23}$	$\frac{21}{24}$
Proteinaceous Casts (D)	$\frac{28}{34}$	$\frac{21}{28}$	$\frac{14}{17}$	$\frac{14}{22}$	$\frac{13}{21}$	$\frac{27}{49}$	$\frac{11}{24}$	$\frac{11}{16}$	$\frac{13}{27}$	$\frac{21}{26}$
Proteinaceous Casts (T)	$\frac{59}{66}$	$\frac{19}{22}$	$\frac{33}{33}$	$\frac{27}{28}$	$\frac{28}{29}$	$\frac{48}{51}$	$\frac{17}{26}$	$\frac{30}{34}$	$\frac{19}{23}$	$\frac{22}{24}$

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Dose Levels (ppm)	0	156	625	2500	10000	0	156	625	2500	10000
Regenerative Epithelium (D)	$\frac{15}{34}$	$\frac{15}{28}$	$\frac{7}{17}$	$\frac{11}{22}$	$\frac{9}{21}$	$\frac{12}{49}$	$\frac{5}{24}$	$\frac{3}{16}$	$\frac{2}{27}$	$\frac{8}{26}$
Regenerative Epithelium (T)	$\frac{57}{66}$	$\frac{21}{22}$	$\frac{32}{33}$	$\frac{26}{28}$	$\frac{26}{29}$	$\frac{30}{51}$	$\frac{14}{26}$	$\frac{17}{34}$	$\frac{13}{23}$	$\frac{15}{24}$
Kidneys										
Chronic Progressive Nephropathy (D)	$\frac{17}{34}$	$\frac{20}{28}$	$\frac{10}{17}$	$\frac{12}{22}$	$\frac{10}{21}$	$\frac{17}{49}$	$\frac{7}{24}$	$\frac{6}{16}$	$\frac{4}{27}$	$\frac{11}{26}$
Chronic Progressive Nephropathy (T)	$\frac{60}{66}$	$\frac{22}{22}$	$\frac{31}{33}$	$\frac{25}{28}$	$\frac{27}{29}$	$\frac{32}{51}$	$\frac{14}{26}$	$\frac{18}{34}$	$\frac{16}{23}$	$\frac{19}{24}$
Tubular Dilatation (D)	$\frac{16}{34}$	$\frac{9}{28}$	$\frac{6}{17}$	$\frac{9}{22}$	$\frac{9}{21}$	$\frac{10}{49}$	$\frac{2}{24}$	$\frac{3}{16}$	$\frac{5}{27}$	$\frac{9}{26}$
Tubular Dilatation (T)	$\frac{37}{66}$	$\frac{9}{22}$	$\frac{10}{33}$	$\frac{11}{28}$	$\frac{13}{29}$	$\frac{6}{51}$	$\frac{1}{26}$	$\frac{3}{34}$	$\frac{5}{23}$	$\frac{6}{24}$
Pelvic Dilatation (D)	$\frac{5}{34}$	$\frac{4}{28}$	$\frac{0}{17}$	$\frac{2}{22}$	$\frac{1}{21}$	$\frac{5}{49}$	$\frac{7}{24}$	$\frac{2}{16}$	$\frac{6}{27}$	$\frac{5}{26}$
Pelvic Dilatation (T)	$\frac{2}{66}$	$\frac{6}{22}$	$\frac{6}{33}$	$\frac{1}{28}$	$\frac{1}{29}$	$\frac{9}{51}$	$\frac{7}{26}$	$\frac{3}{34}$	$\frac{6}{23}$	$\frac{4}{24}$
Stomach										
Diluted Mucosal Glands (D)	$\frac{6}{33}$	$\frac{8}{28}$	$\frac{6}{17}$	$\frac{7}{22}$	$\frac{1}{20}$	$\frac{20}{49}$	$\frac{9}{24}$	$\frac{8}{16}$	$\frac{10}{26}$	$\frac{10}{26}$
Diluted Mucosal Glands (T)	$\frac{46}{66}$	$\frac{16}{22}$	$\frac{23}{33}$	$\frac{17}{28}$	$\frac{14}{29}$	$\frac{39}{51}$	$\frac{20}{26}$	$\frac{27}{34}$	$\frac{16}{23}$	$\frac{21}{24}$
Pancreas										
Chronic Pancreatitis (D)	$\frac{3}{32}$	$\frac{4}{28}$	$\frac{1}{17}$	$\frac{1}{22}$	$\frac{2}{20}$	$\frac{1}{47}$	$\frac{0}{24}$	$\frac{0}{16}$	$\frac{0}{26}$	$\frac{0}{26}$
Chronic Pancreatitis (T)	$\frac{14}{66}$	$\frac{5}{22}$	$\frac{8}{33}$	$\frac{9}{28}$	$\frac{5}{29}$	$\frac{4}{51}$	$\frac{2}{26}$	$\frac{5}{34}$	$\frac{1}{23}$	$\frac{1}{24}$
Mesenteric LN										
Pigmented Macrophages, Increased (D)	$\frac{2}{32}$	$\frac{0}{26}$	$\frac{0}{17}$	$\frac{2}{21}$	$\frac{0}{18}$	$\frac{7}{48}$	$\frac{4}{22}$	$\frac{4}{15}$	$\frac{5}{27}$	$\frac{1}{24}$
Pigmented Macrophages, Increased (T)	$\frac{2}{66}$	$\frac{0}{22}$	$\frac{1}{33}$	$\frac{1}{28}$	$\frac{0}{29}$	$\frac{8}{51}$	$\frac{6}{26}$	$\frac{9}{34}$	$\frac{1}{23}$	$\frac{5}{24}$
Lymphangiectasis (D)	$\frac{0}{32}$	$\frac{0}{26}$	$\frac{0}{17}$	$\frac{0}{21}$	$\frac{0}{18}$	$\frac{2}{48}$	$\frac{0}{22}$	$\frac{0}{15}$	$\frac{1}{27}$	$\frac{0}{24}$
Lymphangiectasis (T)	$\frac{5}{66}$	$\frac{3}{22}$	$\frac{5}{33}$	$\frac{0}{28}$	$\frac{1}{29}$	$\frac{0}{51}$	$\frac{4}{26}$	$\frac{1}{34}$	$\frac{1}{23}$	$\frac{1}{24}$
Testes W/Epidid										
Hypospermia (D)	$\frac{4}{34}$	$\frac{4}{28}$	$\frac{4}{17}$	$\frac{4}{22}$	$\frac{4}{21}$	$\frac{0}{0}$	$\frac{0}{0}$	$\frac{0}{0}$	$\frac{0}{0}$	$\frac{0}{0}$
Hypospermia (T)	$\frac{15}{66}$	$\frac{2}{22}$	$\frac{6}{33}$	$\frac{6}{28}$	$\frac{11}{29}$	$\frac{0}{0}$	$\frac{0}{26}$	$\frac{0}{34}$	$\frac{0}{23}$	$\frac{0}{24}$
Atrophy/Degeneration (D)	$\frac{5}{34}$	$\frac{9}{28}$	$\frac{5}{17}$	$\frac{4}{22}$	$\frac{8}{21}$	$\frac{0}{0}$	$\frac{0}{0}$	$\frac{0}{0}$	$\frac{0}{0}$	$\frac{0}{0}$
Atrophy/Degeneration (T)	$\frac{21}{66}$	$\frac{4}{22}$	$\frac{9}{33}$	$\frac{8}{28}$	$\frac{12}{29}$	$\frac{0}{0}$	$\frac{0}{26}$	$\frac{0}{34}$	$\frac{0}{23}$	$\frac{0}{24}$
Prostate										
Chronic-Active Inflammation (D)	$\frac{25}{34}$	$\frac{18}{28}$	$\frac{12}{17}$	$\frac{10}{22}$	$\frac{9}{21}$	$\frac{0}{0}$	$\frac{0}{0}$	$\frac{0}{0}$	$\frac{0}{0}$	$\frac{0}{0}$
Chronic-Active Inflammation (T)	$\frac{50}{66}$	$\frac{22}{22}$	$\frac{27}{33}$	$\frac{17}{28}$	$\frac{14}{29}$	$\frac{0}{0}$	$\frac{0}{26}$	$\frac{0}{34}$	$\frac{0}{23}$	$\frac{0}{24}$
Ovaries										
Ovarian Cysts (T)	$\frac{0}{0}$	$\frac{0}{0}$	$\frac{0}{0}$	$\frac{0}{0}$	$\frac{0}{0}$	$\frac{8}{51}$	$\frac{2}{26}$	$\frac{8}{34}$	$\frac{4}{23}$	$\frac{4}{24}$
Ovarian Cysts (D)	$\frac{0}{0}$	$\frac{0}{0}$	$\frac{0}{0}$	$\frac{0}{0}$	$\frac{0}{0}$	$\frac{4}{47}$	$\frac{4}{24}$	$\frac{1}{16}$	$\frac{1}{25}$	$\frac{4}{25}$
Paranasal Sinus										
Chronic-Active Inflammation (T)	$\frac{0}{10}$	$\frac{0}{10}$	$\frac{3}{10}$	$\frac{1}{10}$	$\frac{1}{10}$	$\frac{0}{10}$	$\frac{1}{10}$	$\frac{4}{10}$	$\frac{1}{10}$	$\frac{1}{10}$

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<u>Dose Levels (ppm)</u>	<u>0</u>	<u>156</u>	<u>625</u>	<u>2500</u>	<u>10000</u>	<u>0</u>	<u>156</u>	<u>625</u>	<u>2500</u>	<u>10000</u>
<u>Ovaries</u>										
Cystic Ovarian Bursa (D)	$\frac{0}{0}$	$\frac{0}{0}$	$\frac{0}{0}$	$\frac{0}{0}$	$\frac{0}{0}$	$\frac{6}{47}$	$\frac{0}{24}$	$\frac{0}{16}$	$\frac{1}{25}$	$\frac{1}{25}$
Cystic Ovarian Bursa (T)	$\frac{0}{0}$	$\frac{0}{0}$	$\frac{0}{0}$	$\frac{0}{0}$	$\frac{0}{0}$	$\frac{5}{51}$	$\frac{2}{25}$	$\frac{2}{34}$	$\frac{6}{23}$	$\frac{3}{24}$
<u>Uterus</u>										
Dilatation (D)	$\frac{0}{0}$	$\frac{0}{0}$	$\frac{0}{0}$	$\frac{0}{0}$	$\frac{0}{0}$	$\frac{5}{47}$	$\frac{3}{24}$	$\frac{0}{16}$	$\frac{3}{25}$	$\frac{2}{26}$
Dilatation (T)	$\frac{0}{0}$	$\frac{0}{0}$	$\frac{0}{0}$	$\frac{0}{0}$	$\frac{0}{0}$	$\frac{7}{51}$	$\frac{3}{26}$	$\frac{6}{34}$	$\frac{6}{23}$	$\frac{2}{24}$
<u>Mammary Gland</u>										
Duct Ectasia (D)	$\frac{6}{16}$	$\frac{4}{7}$	$\frac{5}{9}$	$\frac{2}{9}$	$\frac{4}{9}$	$\frac{31}{49}$	$\frac{9}{23}$	$\frac{8}{16}$	$\frac{14}{27}$	$\frac{17}{25}$
Duct Ectasia	$\frac{9}{10}$	$\frac{5}{7}$	$\frac{1}{1}$	$\frac{1}{2}$	$\frac{2}{2}$	$\frac{28}{51}$	$\frac{11}{26}$	$\frac{12}{33}$	$\frac{13}{23}$	$\frac{17}{24}$
Acinar Hyperplasia (D)	$\frac{0}{16}$	$\frac{0}{7}$	$\frac{0}{9}$	$\frac{1}{9}$	$\frac{1}{9}$	$\frac{5}{49}$	$\frac{3}{23}$	$\frac{1}{16}$	$\frac{2}{27}$	$\frac{5}{25}$
Acinar Hyperplasia (T)	$\frac{2}{10}$	$\frac{0}{7}$	$\frac{0}{1}$	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{6}{51}$	$\frac{7}{26}$	$\frac{6}{33}$	$\frac{1}{23}$	$\frac{8}{24}$
<u>Sterum W/Marrow</u>										
Marrow Hyperplasia (D)	$\frac{6}{33}$	$\frac{3}{28}$	$\frac{2}{17}$	$\frac{7^*}{22}$	$\frac{8^*}{21}$	$\frac{3}{49}$	$\frac{2}{24}$	$\frac{0}{16}$	$\frac{2}{27}$	$\frac{1}{26}$
Marrow Hyperplasia (T)	$\frac{10}{66}$	$\frac{2}{22}$	$\frac{2}{33}$	$\frac{23^*}{28}$	$\frac{28^*}{29}$	$\frac{1}{51}$	$\frac{1}{26}$	$\frac{1}{34}$	$\frac{1}{23}$	$\frac{0}{24}$
Erythroid Hyperplasia (D)	$\frac{2}{33}$	$\frac{1}{28}$	$\frac{4^*}{17}$	$\frac{6^*}{22}$	$\frac{4^*}{21}$	$\frac{1}{49}$	$\frac{0}{24}$	$\frac{2}{16}$	$\frac{1}{27}$	$\frac{4^*}{26}$
Erythroid Hyperplasia (T)	$\frac{2}{66}$	$\frac{2^*}{22}$	$\frac{9^*}{33}$	$\frac{13^*}{28}$	$\frac{11^*}{29}$	$\frac{0}{51}$	$\frac{1^*}{26}$	$\frac{4^*}{34}$	$\frac{10^*}{23}$	$\frac{9^*}{24}$
Myeloid Hyperplasia (D)	$\frac{4}{33}$	$\frac{1}{28}$	$\frac{0}{17}$	$\frac{3}{22}$	$\frac{0}{21}$	$\frac{4}{49}$	$\frac{7}{24}$	$\frac{1}{16}$	$\frac{6}{27}$	$\frac{2}{26}$
Myeloid Hyperplasia (T)	$\frac{6}{66}$	$\frac{0}{22}$	$\frac{1}{33}$	$\frac{1}{28}$	$\frac{3}{29}$	$\frac{4}{51}$	$\frac{2}{26}$	$\frac{1}{34}$	$\frac{2}{23}$	$\frac{0}{24}$
Distended Marrow Space (D)	$\frac{0}{33}$	$\frac{0}{28}$	$\frac{0}{17}$	$\frac{8^*}{22}$	$\frac{8^*}{21}$	$\frac{0}{49}$	$\frac{0}{24}$	$\frac{0}{16}$	$\frac{0}{27}$	$\frac{0}{26}$
Distended Marrow Space (T)	$\frac{0}{66}$	$\frac{0}{22}$	$\frac{1^*}{33}$	$\frac{20^*}{28}$	$\frac{24^*}{29}$	$\frac{0}{51}$	$\frac{0}{26}$	$\frac{0}{34}$	$\frac{0}{23}$	$\frac{0}{24}$
<u>Harderian GL</u>										
Non-suppurative Adenitis (D)	$\frac{10}{34}$	$\frac{6}{28}$	$\frac{5}{17}$	$\frac{8}{22}$	$\frac{4}{21}$	$\frac{19}{49}$	$\frac{12}{23}$	$\frac{5}{16}$	$\frac{11}{27}$	$\frac{8}{26}$
Non-suppurative Adenitis (T)	$\frac{26}{66}$	$\frac{10}{22}$	$\frac{11}{33}$	$\frac{14}{28}$	$\frac{17}{29}$	$\frac{38}{51}$	$\frac{18}{26}$	$\frac{18}{34}$	$\frac{14}{23}$	$\frac{18}{24}$
<u>Lymph Node, Others</u>										
Lymphoreticular Hyperplasia (D)	$\frac{0}{3}$	$\frac{0}{7}$	$\frac{1}{8}$	$\frac{1}{4}$	$\frac{0}{3}$	$\frac{3}{9}$	$\frac{3}{3}$	$\frac{0}{3}$	$\frac{6}{8}$	$\frac{0}{3}$
Lymphoreticular Hyperplasia (T)	$\frac{8}{25}$	$\frac{0}{4}$	$\frac{4}{10}$	$\frac{3}{6}$	$\frac{3}{6}$	$\frac{2}{5}$	$\frac{4}{7}$	$\frac{0}{1}$	$\frac{0}{0}$	$\frac{0}{2}$
Lymphangiectasis (D)	$\frac{0}{34}$	$\frac{2}{28}$	$\frac{3}{17}$	$\frac{1}{22}$	$\frac{0}{21}$	$\frac{2}{49}$	$\frac{0}{24}$	$\frac{0}{16}$	$\frac{0}{27}$	$\frac{1}{26}$
Lymphangiectasis (T)	$\frac{19}{25}$	$\frac{4}{4}$	$\frac{7}{10}$	$\frac{5}{6}$	$\frac{4}{6}$	$\frac{1}{5}$	$\frac{2}{7}$	$\frac{1}{1}$	$\frac{0}{0}$	$\frac{0}{2}$
<u>Eye</u>										
Chronic-Active Inflammation (D)	$\frac{2}{34}$	$\frac{1}{28}$	$\frac{0}{17}$	$\frac{2}{22}$	$\frac{1}{21}$	$\frac{0}{49}$	$\frac{1}{24}$	$\frac{1}{16}$	$\frac{0}{27}$	$\frac{2}{26}$

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<u>Eye</u>										
Chronic-Active Inflammation (T)	$\frac{0}{66}$	$\frac{0}{22}$	$\frac{1^*}{33}$	$\frac{4^*}{28}$	$\frac{3^*}{29}$	$\frac{0}{51}$	$\frac{0}{26}$	$\frac{0}{34}$	$\frac{1^*}{23}$	$\frac{0}{24}$
<u>Skin</u>										
Necrotizing Ulcerative Dermatitis (D)	$\frac{1}{34}$	$\frac{1}{26}$	$\frac{1}{17}$	$\frac{1}{22}$	$\frac{2}{21}$	$\frac{0}{49}$	$\frac{1}{24}$	$\frac{0}{15}$	$\frac{0}{27}$	$\frac{0}{25}$
Necrotizing Ulcerative Dermatitis (T)	$\frac{18}{65}$	$\frac{7}{22}$	$\frac{12}{33}$	$\frac{6}{28}$	$\frac{13}{29}$	$\frac{2}{51}$	$\frac{1}{26}$	$\frac{1}{34}$	$\frac{1}{23}$	$\frac{0}{24}$
Hyperkeratosis (T)	$\frac{15}{65}$	$\frac{6}{22}$	$\frac{8}{33}$	$\frac{6}{28}$	$\frac{14}{29}$	$\frac{2}{51}$	$\frac{1}{26}$	$\frac{1}{34}$	$\frac{1}{23}$	$\frac{0}{24}$
Hyperkeratosis (D)	$\frac{1}{34}$	$\frac{1}{26}$	$\frac{1}{17}$	$\frac{1}{22}$	$\frac{1}{21}$	$\frac{0}{49}$	$\frac{1}{24}$	$\frac{0}{15}$	$\frac{0}{27}$	$\frac{0}{25}$
Acanthosis (D)	$\frac{2}{34}$	$\frac{2}{26}$	$\frac{1}{17}$	$\frac{1}{22}$	$\frac{1}{21}$	$\frac{0}{49}$	$\frac{1}{24}$	$\frac{0}{15}$	$\frac{0}{27}$	$\frac{0}{25}$
Acanthosis (D)	$\frac{15}{65}$	$\frac{6}{22}$	$\frac{8}{33}$	$\frac{6}{28}$	$\frac{14}{29}$	$\frac{2}{51}$	$\frac{1}{26}$	$\frac{1}{34}$	$\frac{1}{23}$	$\frac{0}{24}$
<u>Thymus</u>										
Cysts (D)	$\frac{0}{23}$	$\frac{1}{23}$	$\frac{0}{15}$	$\frac{0}{16}$	$\frac{0}{15}$	$\frac{10}{41}$	$\frac{2}{20}$	$\frac{2}{14}$	$\frac{5}{19}$	$\frac{6}{19}$
Cysts (T)	$\frac{1}{63}$	$\frac{1}{22}$	$\frac{1}{32}$	$\frac{0}{19}$	$\frac{0}{27}$	$\frac{13}{46}$	$\frac{6}{22}$	$\frac{8}{32}$	$\frac{6}{22}$	$\frac{10}{24}$
<u>Urinary Bladder</u>										
Proteinaceous Material (D)	$\frac{12}{34}$	$\frac{11}{28}$	$\frac{2}{16}$	$\frac{6}{20}$	$\frac{4}{21}$	$\frac{3}{48}$	$\frac{1}{23}$	$\frac{0}{15}$	$\frac{1}{24}$	$\frac{0}{24}$
Proteinaceous Material (T)	$\frac{32}{66}$	$\frac{14}{22}$	$\frac{18}{33}$	$\frac{10}{28}$	$\frac{9}{29}$	$\frac{5}{51}$	$\frac{0}{25}$	$\frac{3}{34}$	$\frac{2}{23}$	$\frac{4}{24}$

* Noticeable increase of incidence rate (%); (D) - Animals found in unscheduled deaths; (T) - Animals sacrificed at terminal sacrifices.

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Evaluation and Conclusions:

1. There were no unusual changes in mortality, body weights, food consumption, and clinical signs over the course of this study attributable to the administration of Diflubenzuron.
2. Although the methemoglobin and sulfhemoglobin levels of treated animals appeared to show general trend of decline except in the high dose female groups at the end of 104 weeks (Results No. 5 c), the test compound persistently induced the dose-related elevation of methemoglobin and sulfhemoglobin levels in the treated animals of both sexes at the dose levels tested (156 through 10000 ppm). Methemoglobinemia and sulfhemoglobinemia are known to impair oxygen transport capability of the blood with consequent peripheral hypoxia and other cardiac effects. Therefore, the no-observed-effect level of Diflubenzuron for methemoglobinemia and sulfhemoglobinemia in rats should be established in this study. Furthermore, methemoglobinemia refers to the clinical condition in which over 1% of the hemoglobin of the peripheral blood is in the methemoglobin formation. The results of this study should be expressed in terms of the available hemoglobin being transformed into methemoglobin.
3. Treatment-related histomorphologic lesions were observed in the section of spleen, liver, and bone marrow of treated animals. Increased pigmented-macrophages were found in the spleen and liver of treated rats of both sexes (156 through 10000 ppm). The pigmented macrophages appeared to be the cause of increase in the amount of iron (ferritin micelles) in these organs. These results were substantiated by the significant decrease of hemoglobin levels in the treated animals of both sexes at week 52. In addition, the increased incidences of pathological changes in the spleen and liver in animals of both sexes treated with 2500 and 10000 ppm Diflubenzuron correlated well with the statistically significant increases in the spleen and liver weights of the same female and male groups. The increased incidences of marrow hyperplasia, erythroid hyperplasia and distended marrow space were observed in the males treated with 2500 and 10000 ppm Diflubenzuron. The incidence of erythroid hyperplasia was also increased with dose in females treated with 625, 2500, and 10000 ppm Diflubenzuron. These results were also correlated well with the decreased ratio of M:E (Myeloid:Erythroid) cells which indicated the abnormal state of bone marrow found in the treated groups of both sexes (2500 and 10000 ppm).
4. The frequently observed nonneoplastic lesions ~~that~~ were sporadically distributed among the treated and untreated rats ~~that~~ had no dose-related positive trend and are summarized in the Results No. 10. However, the increased incidences of thrombus in the heart, congestion/hemorrhage in the spleen, chronic-active inflammation in the paranasal sinus, and chronic-active inflammation in the eye found in the treated animals cannot be evaluated properly without the historical control data of the Sprague-Dawley rats. No other nonneoplastic lesions in a variety of organ tissues from treated animals of both sexes were considered to be significantly different from the control groups.

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5. Neoplastic lesions ~~that~~ were sporadically distributed among the treated and untreated rats ~~that~~ had no dose-related positive trend and are summarized in the Results No. 9. No neoplastic lesions in a variety of organ tissues from treated animals of both sexes were considered to be significantly different from the control groups.

6. Classification of Data: Supplementary

The reporting deficiencies for this study cited in our conclusion #2 and #4 should be clarified immediately. The study may be upgraded with submission of this information.

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