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TXR-4075

10-5-84

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

004075

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

October 5, 1984

Subject: Diflubenzuron 6F1832: Review of the Lifetime Oncogenic Study of Diflubenzuron in Mice and Request for Deleting Some Precautionary Label Statements
Accession No. 253570, 253571, 253572, 253573, 253574, 253575, and 253576. Caswell No. 346A.

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

Thru: David Ritter, Acting 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)

Toxicology Branch Recommendation:

1. The registrant should be apprised of the deficiencies in the lifetime oncogenicity study of Diflubenzuron in mice, Huntingdon Research Center Report No. PDR 360/831096/B, May 15, 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 of the Life Time Oncogenic Study of Diflubenzuron in Mice (Huntingdon Research Center Report No. PDR 360/831096/B, May 15, 1984 - Total Duration of Dietary Intake: 91 Weeks)

Procedure:

The procedures used in the lifetime oncogenicity study of Diflubenzuron in the HC/CFLP mice are identical to those described previously in the 52-week Interim Report (HRC Report No. 360/821141, 56645/18/83, Accession No. 250270, 250271, and 250272).

Results:

1. Clinical Signs

The blue/gray discoloration of the extremities and dark eyes found in the treated animals during the first year of study have been previously recorded in the interim 52-week report. No other changes in the incidental clinical-signs were observed in animals of all groups during the second year of this study (52-91 weeks).

2. Mortality

Dose Group (ppm)	No. of Animals (dead/tested)* Males	Females
0	40/104	44/104
16	12/52	24/52
80	17/52	27/52
400	25/52	19/52
2000	14/52	30/52
10000	17/52	23/52

* Main group

Findings: No obvious treatment-related-effect on mortality was observed during the 1-78 weeks of study.

3. Body Weights

Dose Group (ppm)	Mean Weekly Body Weights (g) (Weeks) 1	26	52	78	92
(Males)					
0	37	57	67	67	66
16	38	59	67	67	62
80	38	58	65	67	69
400	39	58	65	66	64
2000	39	58	65	66	66
10000	38	57	64	64	63
(Females)					
0	33	47	54	56	61
16	33	49	57	59	62
80	33	49	58	60	56
400	33	48	56	59	53
2000	33	48	56	58	61
10000	33	48	55	56	56

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3. Body Weights - Continued

Findings: There were no significant differences in the mean body weight values between the treated and control groups (both sexes) during the study.

4. Food Consumption

Dose Group (ppm)	Mean Weekly Food Consumption Values (g) (Weeks) 1	26	52	78	92
(Males)					
0	30	32	34	36	36
16	31	32	32	36	36
80	31	32	33	37	40
400	30	30	32	38	42
2000	31	31	35	39	42
10000	30	32	34	38	40
(Females)					
0	27	29	33	38	38
16	28	30	31	38	44
80	30	29	33	39	40
400	29	30	30	38	34
2000	30	30	33	44	39
10000	30	31	32	41	43

Findings: No significant differences in the mean weekly food consumption values were observed between the treated and control groups (both sexes) during the study.

5. Hematology

(a) Mean Clinical Hematology Values of Male Mice at Week 91

Dose (ppm)	0	16	80	400	2000	10000
PCV (%)	41.0	39.0	42.0	42.0	37	36*
Hb (g%)	13.9	13.0	13.2	14.0	12.4	13.0
RBC (10^6/CMM)	7.3	6.8	7.2	7.6	6.0*	6.3*
MCHC (%)	33.5	33.5	31.5	33.1	33.0	36.6*
MCH (Pg)	19.1	19.2	18.4	18.8	20.8*	20.7*
MCV (fl)	58.0	58.0	59.0	57.0	64.0	56.0
WBC (10^3/CMM)	7.1	4.0	7.5	12.4	8.9	6.3
Plats (10^3/CMM)	1155	1296	1305	1413*	1484*	1368*
S-Hb (% H_b)	0.10	0.13	0.34*	1.27*	3.45*	4.06*
Met-Hb(% Hb)	1.36	1.38	1.78*	2.96*	4.27*	5.92*

*Significant changes: PCB - Packed Cell Volume; Hb - Hemoglobin; RBC - Red Blood Cell; MCHC - Mean Corpuscular Hemoglobin Concentration; MCH - Mean Corpuscular Hemoglobin: MCV - Mean Corpuscular Volume; WBC - White Blood Cell; Plats - Platelet; S-Hb - Sulfhemoglobin; Met-Hb - Methemoglobin.

5. Hematology - Continued

Findings for Male Mice: The mean PCV values and RBC counts were decreased in the 2000 and 10000 ppm level groups at week 52 and a similar trend of decrease in these values was also observed in the same level groups at week 91. The mean corpuscular hemoglobin concentration and the mean corpuscular hemoglobin were found to be consistently higher in the 2000 and 10000 ppm level groups from the week 52 to week 91 when compared with that of the control group. There was a treatment-related increase in the platelet count among mice treated with 400, 2000, and 10000 level groups in weeks 26, 52, 78, and 91. The Heinz Bodies were also detected in samples from mice treated with 2000 and 10000 ppm level groups in weeks 52, 78, and 91. A dose-related elevation of methemoglobin and sulfhemoglobin was consistently observed in weeks 26, 52, 78 and 91.

(b) Mean Clinical Hematology Values of Female Mice at Week 91

Dose (ppm)	0	16	80	400	2000	10000
PCV (%)	42.0	44.0	43.0	44.0	41.0	40.0
Hb (g%)	13.7	14.0	14.1	14.7	13.8	14.2
RBC (10^6/CMM)	7.5	7.6	7.8	7.5	7.0	6.7*
MCHC (%)	32.4	31.8	32.5	33.5	34.0	35.9*
MCH (Pg)	18.4	18.6	18.1	19.6*	19.8*	21.1*
MCV (fl)	57.0	58.0	56.0	59.0	58.0	59.0
WBC (10^3/CMM)	5.4	5.7	8.2	8.7	8.9	8.8
Plats (10^3/CMM)	791	916	690	1315*	1446*	1457*
Met - Hb (%Hb)	0.77	0.89	1.43*	2.76*	4.36*	5.4*
S - Hb (%Hb)	0.12	0.12	0.22	1.75*	3.94*	3.6*

* Significant changes

Findings for Female Mice: The mean PCV values for the 2000 and 10000 ppm level groups were significantly lower than that of the control group at week 52. But, no significant difrerence in these values was observed in the same treated groups at week 91 when compared with that of the control group. The mean RBC counts were significantly decreased in the 2000 and 10000 ppm level groups at week 52. But, significant decrease in these values was only observed in the 10000 ppm level group at week 91. The MCHC and the MCH values were found to be consistently higher in the 10000 ppm level group when compared with that of the control group from the week 52 to week 91. There was a treatment-related increase in the platelet count among mice treated with 400, 2000, and 10000 ppm Dimilin in weeks 26, 52, 78, and 91. The Heinz Bodies were found consistently in samples from mice treated with 2000 and 10000 ppm Dimilin in weeks 52, 78 ad 91. A dose-related elevation of methemoglobin and sulfhemoglobin was consistently observed in weeks 26, 52, 78 and 91.

5. Hematology - Continued

(c) Methemoglobin and Sulfhemoglobin Values at the Week 52, 78 and 91

Dose (ppm)	0	16	80	400	2000	10000
Males						
Metheme (52 Week)	0.57	0.84*	1.54*	3.25*	4.11*	6.38*
" (78 ")	0.66	0.87	1.37*	2.34*	3.17*	4.63*
" (91 ")	1.36	1.38	1.78*	2.96*	4.27*	5.92*
Sulfheme (52 Week)	0.27	0.61*	1.55*	3.30*	4.03*	6.32*
" (78 ")	0.12	0.17	0.41*	4.01*	3.75*	6.35*
" (91 ")	0.10	0.13	0.34*	1.27*	3.45*	4.06*
Females						
Metheme (52 Week)	0.45	0.63	1.13*	2.45*	5.06*	6.25*
" (78 ")	1.34	1.35	1.88*	3.62*	5.18*	6.04*
" (91 ")	0.77	0.89	1.43*	2.76*	4.36*	5.40*
Sulfheme (52 Week)	0.21	0.46*	1.40*	3.17*	6.33*	8.36*
" (78 ")	0.13	0.61	0.59*	3.01*	3.52*	5.72*
" (91 ")	0.12	0.12	0.22	1.75*	3.94*	3.60*

* Significantly dose-related increase

6. Blood Chemistry

Significantly higher Alkaline Phosphatase (AP) activities, Glutamic-Pruvic Transamiinase (GPT) activities and Cholestrol values were observed in weeks 24 and 50 for mice treated with 10000 ppm of Diflubenzuron. But, in week 89, no significant incresae in these enzymatic activities was found in the same treated group except the marginal increase of cholestrol values in male mice. The AP activities, the GPT activities, and Cholestrol value among female mice continued to show no sign of treatment-related effects at week 89. No treatment-related effects on other parameters (i.e., glucose, protein, albumin, urea nitrogen, and glutamic-oxaloacetic transminase activity) were observed during the study.

7. Urinalysis

There were no significant differences in mean (group) urinalysis values (i.e., pH, specific gravity, and protein) between the treated and control groups of both sexes in weeks 51 and 90.

8. Gross Pathology

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

Macropathology	Males (ppm)						Females (ppm)					
	0	16	80	400	2000	10000	0	16	80	400	2000	10000
No. Examined	67	29	33	36	31	36	79	36	41	36	45	42
No. Not Remarkable:												
Stomach												
Mass	-	1	-	-	-	-	-	-	1	1	1	-
Limiting Ridge Prominent/Thickened	21	8	6	6	10	13	32	9	14	8	8	11
*Liver												
*Mass/Nodule	16	9	8	15	10*	16*	5	5	6	2	4*	6*
*Enlarged	19	7	9	5	9*	15*	14	7	12	9	14*	9*
Pale	14	4	5	7	8	7	17	10	6	13	6	9
Surface Irregular/ Pitted	5	3	2	1	2	6	13	7	5	4	9	11
*Lungs												
Mass/Nodule	11	2	7	8	3	6	12	6	6	8	6	6
*Congested	5	2	5*	4	2	7*	5	3	3	6	9*	7*
Kidneys												
Enlarged	11	5	8	6	6	4	6	-	4	2	3	3
Uniform Cortical Scarring	3	4	6	4	4	5	10	1	4	3	2	5
Lymph Nodes												
Regionally Enlarged/ Congested/Cystic	15	10	11	10	11	7	27	9	9	7	12	8
Generally Enlarged/ Congested/Cystic	16	3	3	2	6	7	13	10	14	4	13	8
*Spleen												
*Enlarged	34	17	18	18	26*	30*	53	23	30	24	40*	37*
*Dark	-	-	-	-	1*	3*	-	-	-	-	2*	1*
Heart												
Enlarged	2	1	-	1	2	2	4	-	2	-	-	3
Adrenals												
Enlarged	1	-	-	-	-	-	5	1	6	3	2	3
Pituitary												
Enlarged	-	1	-	-	-	1	6	4	2	5	2	2
Urinary Bladder												
Mass	-	-	-	1	-	-	4	1	1	-	-	1
Testis												
Mass	1	1	-	1	-	1	0	0	0	0	0	0
Seminal Vesicle												
Distended/Enlarged	5	4	5	3	3	1	0	0	0	0	0	0
*Ovaries												
Mass	0	0	0	0	0	0	9	3	2	3	3	1
*Enlarged	0	0	0	0	0	0	3	1	2	1	5*	4*

8. Gross Pathology - Continued

Macropathology	Males (ppm)						Females (ppm)					
	0	16	80	400	2000	10000	0	16	80	400	2000	10000
Uterus												
Mass	0	0	0	0	0	0	6	6	3	3	5	4
Thymus												
Enlarged	1	1	3	-	1	1	1	1	3	1	3	2
*Skin												
*Cyanosis	-	-	-	1	6*	4*	-	-	-	1	2*	3*
Subcutis												
Mass	2	2	1	1	2	-	4	1	3	-	2	2
Thoracic cavity												
Mass	9	1	1	4	-	4	10	6	7	7	1	3

8. Gross Pathology - Continued

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

Macropathology	Males (ppm)						Females (ppm)					
	0	16	80	400	2000	10000	0	16	80	400	2000	10000
No. Examined	37	22	19	16	21	16	25	16	11	16	7	10
No. Not Remarkable:												
Stomach												
Mass	1	-	1	-	1	-	-	-	-	-	-	1
Limiting Ridge Prominent/Thickened	2	2	2	1	-	-	1	1	-	1	-	2
*Liver												
Mass/Nodule	13	8	9	8	7	5	2	1	3	2	2	1
*Enlarged	2	-	3	1	4*	6*	1	1	-	1	-	4*
Pale	-	-	2	1	2	4	2	-	-	1	-	1
Surface Irregular/ Pitted	1	1	1	-	1	3	4	2	1	1	1	4
*Lungs												
Mass/Nodule	9	10	4	6	8	4	5	4	-	6	3	3
*Congested	-	-	2*	-	1*	1*	-	-	-	-	-	-
Kidneys												
Enlarged	1	-	1	1	1	-	3	-	1	-	-	-
Uniform Cortical Scarring	2	-	1	4	1	3	1	-	1	-	-	1
Lymph Nodes												
Regionally Enlarged/ Congested/Cystic	6	3	5	1	1	3	3	3	2	3	1	-
Generally Enlarged/ Congested/Cystic	1	1	1	-	1	-	1	-	-	-	-	-
*Spleen												
*Enlarged	11	8	10	10	14*	10*	9	6	6	9	5*	9*
*Dark	-	-	-	3	13*	13*	-	-	-	2*	-	10*
Heart												
Enlarged	-	1	-	-	1	-	2	-	-	2	-	-
Adrenals												
Enlarged	-	-	-	-	-	-	-	1	-	1	-	-
Pituitary												
Enlarged	-	-	-	1	-	1	2	5	1	1	-	-
Testis												
Mass	-	1	-	-	2	-	0	0	0	0	0	0
Seminal Vesicle												
Distended/Enlarged	11	4	11	6	8	3	0	0	0	0	0	0
Ovaries												
Mass	0	0	0	0	0	0	1	-	-	-	-	-
Enlarged	0	0	0	0	0	0	3	-	1	2	-	1
Uterus												
Mass	0	0	0	0	0	0	2	-	-	-	1	-
Thymus												
Enlarged	-	-	-	-	-	-	-	-	-	-	-	-
*Skin												
*Cyanosis	-	-	1	14*	21*	16*	-	-	-	5*	7*	10*
Subcutis												
Mass	1	-	2	2	-	-	-	-	-	-	-	-
Thoracic cavity												
Mass	-	-	-	-	-	-	1	-	-	-	-	1

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8. Gross Pathology - Continued

(c) Summary of Gross Pathology Findings:

a) For Animals Dying Prior to Study Termination

There were increased incidences of enlarged livers, livers with nodule or mass, congested lungs, splenic enlargement, dark discoloration of the spleen, and cyanosis of the cutis in animals of both sexes treated with 2000 and 10000 ppm Diflubenzuron. The enlarged ovaries were also noted among females treated at 2000 and 10000 ppm. No other pathological findings were found to be significant in this study.

b) For Animals Sacrificed at Study Termination

Increased incidences of splenic enlargement, dark discoloration of the spleen, and cyanosis of the cutis were persistently observed in animals of both sexes treated wth 2000 and 10000 ppm Diflubenzuron. Enlarged livers were also found in animals treated at 10000 ppm. Congested lungs were noted only among males treated with Diflubenzuron. No other pathological findings were found to be significant at terminal sacrifice.

rgan Weights

Mean Values (g) for Animals Killed at Termination

ns	Males (ppm)						Females (ppm)					
	0	16	80	400	2000	10000	0	16	80	400	2000	10000
Weight	64	61	65	62	64	61	54	59	53	53	54	52
n	0.43	0.42	0.43	0.43	0.43	0.42	0.45	0.43	0.44	0.44	0.45	0.46
itary (mg)	3.9	3.8	3.6	3.7	3.8	3.84	5.5	6.3	4.1	4.5	4.2	4.5
t	0.32	0.31	0.33	0.33	0.34	0.36	0.25	0.25	0.23	0.24	0.26	0.27
s	0.35	0.38	0.38	0.36	0.33	0.33	0.31	0.30	0.29	0.34	0.34	0.38
r	3.49	3.08	4.09	3.78	4.26*	5.01*	3.09	3.10	2.86	2.89	3.41*	3.52*
en	0.29	0.31	0.54	0.36	0.38*	0.44*	0.30	0.30	0.40	0.40	0.47*	0.44*
us (mg)	37.2	37.6	38.2	40.2	30.6	30.0	38.1	35.1	32.5	36.0	31.5	38.2
ey	1.09	1.07	1.18	1.17	1.16	1.14	1.15	0.8	0.77	0.72	0.67	0.78
oid (mg)	9.7	9.3	9.6	10.3	10.5	9.7	12.0	12.5	13.1	9.5	12.2	14.1
nal (mg)	8.9	8.7	9.8	8.5	9.5	10.2	16.6	17.9	17.4	16.8	16.7	17.5
ds	0.38	0.36	0.41	0.35	0.43	0.45	26.1	17.5	21.5	21.8	24.3	23.4
rease	0.30	0.30	0.33	0.29	0.31	0.28	0.31	0.29	0.27	0.29	0.28	0.29

Significant increase

ndings: Although no treatment-related effect on liver weights and spleen ights among treated mice was demonstrated, the increased spleen weights and ver weights from the treated mice of both sexes receiving 2000 and 10000 ppm flubenzuron were significantly higher than those of the control groups at e terminal kill.

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Individual Histopathological Findings Related to the Neoplastic Lesions for Animals Found Dead or Sacrificed in Extremis During the Weeks 1-94

Dose Levels (ppm)	Males						Females					
	0	16	80	400	2000	10000	0	16	80	400	2000	10000
*Lymphoreticular Tumour												
Lymphosarcoma (D)	29/67	6/29	12/33	10/36	12/31	12/36	33/79	12/36	18/41	9/36	16/45	14/42
" (T)	3/37	3/23	3/19	2/16	3/21	1/16	3/25	1/16	3/11	2/16	0/7	1/10
*Reticulum Cell Sarcoma(D)	6/67	4/29	2/33	1/36	3/31	6/36	6/79	3/36	5/41	6/36	7/45	1/42
* " (T)	5/37	1/23	5/19	0/16	1/21	1/16	2/25	1/16	0/11	2/16	0/7	0/10
Lymphoid Leukaemia (D)	0/37	2/29	1/33	0/36	0/31	0/36	3/79	3/36	0/41	2/36	2/45	1/42
*Lungs												
*Pulmonary Adenocarcinoma(D)	7/67	3/29	7/33	6/36	1/31	0/36	5/79	5/36	5/41	4/36	4/45	4/42
* " " (T)	7/37	9/23	4/19	2/16	6/21	2/16	3/25	2/16	0/11	5/16	3/7	3/10
*Pulmonary Adenoma (D)	0/67	0/29	0/33	0/36	1/31	2/36	2/79	1/36	0/41	2/36	1/45	2/42
* " " (T)	0/37	1/23	0/19	1/16	0/31	0/16	0/25	0/16	1/11	1/16	0/7	0/10
Liver												
Malignant Liver Cell Tumour (D)	5/67	3/29	3/33	4/36	6/31	4/36	0/79	0/36	0/41	1/36	0/45	2/42
Malignant Liver Cell Tumour (T)	3/37	2/23	2/19	5/16	3/21	1/16	0/25	0/16	0/11	0/16	0/7	0/10
Benigh Liver Cell Tumour (D)	3/67	1/29	2/33	4/36	3/31	2/36	0/79	1/36	1/41	1/36	0/45	0/42
" " " " (T)	4/37	4/23	3/19	2/16	0/21	2/16	1/25	0/16	1/11	0/16	1/7	0/10
Haemangioma (D)	6/67	2/29	4/33	5/36	4/31	2/36	2/79	2/36	2/41	1/36	2/45	4/42
" (T)	6/37	4/23	3/19	2/16	4/21	2/16	1/25	1/16	0/11	0/16	0/7	0/10
Lymph Nodes												
Haemangiosarcoma (D)	0/67	0/29	1/33	0/36	0/31	0/36	0/79	0/36	0/41	0/36	0/45	0/42
Haemagioma (T)	1/37	0/23	1/19	0/16	0/21	0/16	0/25	0/16	0/11	0/16	1/7	0/10
Kidneys												
Renal Adenocarcinoma (D)	0/67	1/29	0/33	0/36	0/31	0/36	[illegible]	0/36	0/41	0/36	0/45	0/42
Renal Adenoma (D)	0/0	0/0	0/0	0/0	0/0	0/0	0/79	[illegible]	0/41	0/36	1/45	0/42
Testes												
Interstitial Cell Adenoma(D)	1/67	0/29	1/33	2/36	0/31	0/36	0/0	0/0	0/0	0/0	0/0	0/0
" " " (T)	3/37	3/23	1/19	1/16	2/21	2/16	0/0	0/0	0/0	0/0	0/0	0/0
Seminoma (T)	0/37	0/23	0/19	0/16	0/21	1/16	0/0	0/0	0/0	0/0	0/0	0/0

Histopathological Findings to the Neoplastic Lesions - Continued

se Levels (ppm)	Males 0	16	80	400	2000	10000	Females 0	16	80	400	2000	10000
drenals												
Phaeochromocytoma (D)	1/67	0/29	0/33	0/36	1/31	2/36	1/79	0/36	0/41	0/36	0/45	0/42
" (T)	0/37	0/23	0/19	0/16	0/21	0/16	0/0	0/0	0/0	0/0	0/0	0/0
ortical Adenoma (D)	1/67	0/29	0/33	1/36	1/31	0/36	0/0	0/0	0/0	0/0	0/0	0/0
" " (T)	1/37	1/23	1/19	0/16	0/21	0/16	0/0	0/0	0/0	0/0	0/0	0/0
tomach												
Squamous Cell Papilloma (D)	0/0	0/0	0/0	0/0	0/0	0/0	0/79	0/36	1/41	2/36	3/45	0/42
Squamous Cell Papilloma (T)	1/37	0/23	1/19	0/16	2/21	0/16	1/25	1/16	0/11	0/16	0/7	1/10
keletal Muscle												
Haemangioma (D)	0/67	1/29	1/33	0/36	0/31	0/36	0/0	0/0	0/0	0/0	0/0	0/0
kin/Subcutis												
Subcutaneous Haemangiosarcoma (D)	0/67	0/29	0/33	0/36	1/31	0/36	0/0	0/0	0/0	0/0	0/0	0/0
Subcutaneous Haemangioma (D)	1/67	1/29	0/33	1/36	0/31	0/36	0/0	0/0	0/0	0/0	0/0	0/0
Subcutaneous Haemangioma (T)	1/37	0/23	0/19	2/16	0/21	0/16	0/0	0/0	0/0	0/0	0/0	0/0
Subcutaneous Fibrosarcoma (D)	1/67	0/29	0/33	1/36	0/31	0/36	0/25	1/16	0/11	0/16	0/7	0/10
Subcutaneous Fibrosarcoma (T)	1/37	0/23	0/19	1/16	0/21	0/16	0/0	0/0	0/0	0/0	0/0	0/0
Squamous Cell Papilloma (D)	0/0	0/0	0/0	0/0	0/0	0/0	0/79	0/36	1/41	0/36	0/45	1/42
Squamous Cell Carcinoma (D)	0/0	0/0	0/0	0/0	0/0	0/0	0/79	0/36	1/41	1/36	0/45	1/42
Pituitary												
Adenoma (D)	0/67	2/19	0/33	0/36	0/31	0/36	3/79	2/36	0/41	3/36	1/45	1/42
" (T)	0/0	0/0	0/0	0/0	0/0	0/0	2/25	3/16	0/11	0/16	0/7	0/10
Harderlin Gland												
Adenoma (D)	1/67	1/29	0/33	1/36	0/31	0/36	1/79	0/36	1/41	0/36	0/45	0/42
Adenocarcinoma (D)	0/0	0/0	0/0	0/0	0/0	0/0	0/79	0/36	0/41	0/36	1/45	0/42
Adipose Tissue												
Haemingioma (D)	1/67	0/29	0/33	0/36	1/31	0/36	1/79	0/36	0/41	0/36	0/45	0/42
Spleen												
Haemangiosarcoma (D)	0/0	0/0	0/0	0/0	0/0	0/0	0/79	0/36	1/41	0/36	0/45	0/42
" (T)	0/0	0/0	0/0	0/0	0/0	0/0	0/25	0/16	1/11	0/16	0/7	0/10

10. Histopathological Findings to the Neoplastic Lesions - Continued

Dose Levels (ppm)	Males						Females					
	0	16	80	400	2000	10000	0	16	80	400	2000	10000
Uterus												
Haemangiosarcoma (D)	0/0	0/0	0/0	0/0	0/0	0/0	2/79	0/36	1/41	0/36	0/45	0/42
Haemangioma (D)	0/0	0/0	0/0	0/0	0/0	0/0	1/79	1/36	0/41	0/36	0/45	1/42
" (T)	0/0	0/0	0/0	0/0	0/0	0/0	1/25	0/16	1/11	0/16	0/7	0/10
Uterine Adenocarcinoma (D)	0/0	0/0	0/0	0/0	0/0	0/0	0/79	0/36	0/41	0/36	0/45	1/42
" " (T)	0/0	0/0	0/0	0/0	0/0	0/0	0/25	0/16	0/11	1/16	0/7	0/10
Leiomyoma (D)	0/0	0/0	0/0	0/0	0/0	0/0	0/79	0/36	0/41	0/35	0/45	1/42
" (T)	0/0	0/0	0/0	0/0	0/0	0/0	0/25	0/16	0/16	0/16	1/7	0/10
Ovaries												
Malignant Granulosa Cell Tumour (D)	0/0	0/0	0/0	0/0	0/0	0/0	0/79	0/36	0/41	1/36	0/45	0/42
Granulosa Cell Tumour (D)	0/0	0/0	0/0	0/0	0/0	0/0	1/79	1/36	1/41	2/36	2/45	3/42
Granulosa Cell Tumour (T)	0/0	0/0	0/0	0/0	0/0	0/0	3/25	0/16	0/11	0/16	0/7	0/10
Cervix												
Fibrosarcoma (D)	0/0	0/0	0/0	0/0	0/0	0/0	0/79	0/36	0/41	0/36	1/45	0/42
Thyroid												
Follicular Adenoma (D)	0/0	0/0	0/0	0/0	0/0	0/0	0/79	0/36	0/41	0/36	1/45	0/42
Mammary Gland	0/0	0/0	0/0	0/0	0/0	0/0	2/79	1/36	3/41	0/36	0/45	1/42
Mammary Adenocarcinoma (D)	0/0	0/0	0/0	0/0	0/0	0/0	0/79	0/36	1/41	0/36	0/45	0/42
Mammary Fibrosarcoma (D)												

* Noticeable increase of incidence rate (%); (D) - Interim kill after 52 weeks of treatment; (T) - Terminal Kill.

10. Histopathological Findings to the Neoplastic Lesions - Continued

Summary of Neoplastic Findings:

The analysis of tumour data was based on the time-to-tumour method recommended by the International Agency for Research on Cancer (IARC, 1980). The results of the statistical analyses were initially assessed by calculating the P-values of the corrected Chi-Square in response over all the treated and control groups. If the significant level indicated a significant positive trend ($P<0.05$) or indicated a negative trend ($P>0.95$), the data were further examined by the statistical method of individual pair-wise comparisons. The following tumour types found in 5 or more mice of the same sex were selected for the statistical analyses.

a) Reticulum Cell Sarcoma (RCS)

A significant negative trend ($P=0.95$) for RCS was found in the treated female groups. However, there was no signficant difference in the incidence of this tumour type observed between the treated and control mice ($P = 0.06$ to 0.86).

b) Pulmonary Adenoma or Adenocarcinoma

A significant negative trend ($P=0.98$) for Pulmonary Adenoma or Adenocarcinoma was detected in the treated male groups. No significant difference in the incidence of this tumour type was found between the treated and control mice ($P = 0.11$ to 0.81).

c) Phaeochromocytoma

A significant positive trend ($P=0.0014$) for Phaeochromocytoma was detected in the treated male groups. However, this result was not significant when compared directly with the control group ($P = 0.12$ to 0.50).

d) Squamous Cell Papilloma (SCP)

A marginally negative trend ($P=0.52$) for SCP was observed in the treated female groups. However, there was no significant difference in the incidence of this tumour type found between the treated and control mice at terminal kill.

Reference:

WHO International Agency for Research on Cancer (1980). Long-term and short-term screening assays for carcinogens: A critical appraisal. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Annex: R. Peto et al. Guidelines for simple sensitive experiments. Supplement 2. pp. 311-426.

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11. Individual Histopathological Findings Related to the Nonneoplastic Lesions for Animals Found Dead or Sacrificed in Extremis During the Weeks 1-94

Dose Levels (ppm)	Males 0	16	80	400	2000	10000	Females 0	16	80	400	2000	10000
Heart												
Myocarditis (D)	0/20	0/10	0/11	0/10	0/11	0/10	0/18	0/8	0/10	0/11	0/11	0/11
" (T)	0/37	0/23	0/19	0/16	0/21	0/16	0/25	0/16	0/11	0/16	0/7	0/10
*Lungs												
Peribronchiolar Lymphoid Aggregates (D)	0/20	1/10	1/11	0/10	1/11	1/10	0/18	0/8	1/10	1/11	0/11	0/11
Peribronchiolar Lymphoid Aggregates (T)	1/37	0/23	1/19	0/16	1/21	0/16	0/25	0/16	0/11	0/16	0/7	0/10
Chronic Pneumonitis (D)	3/20	1/10	0/11	0/10	1/11	0/10	1/18	1/8	0/10	1/11	1/11	0/11
*Chronic Pneumonitis (T)	7/37	6/23	5/19	7/16	9/21	5/16	12/25	7/16	4/11	2/16	1/7	2/10
Perivascular Lymphoid aggregations (D)	0/20	1/10	0/11	0/10	0/11	0/10	2/18	0/8	1/10	0/11	1/11	0/11
Perivascular Lymphoid aggregations (T)	1/37	0/23	0/19	0/16	0/21	2/16	2/25	0/16	0/11	1/16	0/7	0/10
Chronic Pneumonia (D)	0/20	0/10	0/11	1/10	0/11	0/10	0/18	0/8	0/10	0/11	0/11	0/11
" " (T)	2/37	0/23	1/19	0/16	0/21	2/16	0/25	0/16	0/11	1/16	0/7	1/10
Brown Pigmented Alveolar Macrophages (D)	1/20	0/10	0/11	0/10	0/11	0/10	0/18	0/8	0/10	0/11	0/11	0/11
Brown Pigmented Alveolar Macrophages (T)	2/37	1/23	1/19	0/16	1/21	0/16	0/25	0/16	0/11	1/16	1/7	0/10
Adenomatosis (D)	1/20	0/10	0/11	0/10	0/11	0/10	0/18	0/8	0/10	0/11	0/11	0/11
" (T)	1/37	3/23	0/19	2/16	0/21	0/16	0/25	0/16	0/10	0/16	0/7	0/10
Thymus												
Medullary Hyperplasia (D)	0/20	0/9	0/10	0/10	0/11	0/10	0/18	2/7	0/9	0/11	0/11	0/11
" " (T)	2/37	1/20	0/18	1/14	1/19	0/11	3/23	4/14	0/10	3/14	1/6	0/10
Lymph Nodes												
Lymphoid Hyperplasia (D)	2/20	0/10	0/11	1/10	0/11	0/10	0/18	1/8	0/10	0/11	0/11	0/11
" " (T)	4/37	3/23	5/19	1/16	1/21	3/16	0/24	0/16	1/11	3/16	0/7	0/10
Cystic Degeneration (T)	1/37	1/23	3/19	0/16	2/21	0/16	5/24	5/16	2/11	2/16	0/7	0/10
" " (D)	0/20	0/10	0/11	0/10	0/11	0/10	1/18	1/8	1/10	0/11	0/11	0/11
Spleen												
*Extramedullary Haemopoiesis (D)	1/20	0/10	0/11	4/10	3/11	3/10	0/18	1/8	0/10	2/11	3/11	7/11
*Extramedullary Haemopoiesis (T)	4/37	2/23	6/19	4/16	6/21	9/16	7/25	4/16	1/11	5/16	5/7	5/10
*No. of Siderocytes (D)	0/20	0/10	0/11	5/10	8/11	9/10	0/18	0/8	0/10	0/11	8/11	10/11

11. Histopathological Findings to the Nonneoplastic Lesions - Continued

Dose Levels (ppm)	Males 0	16	80	400	2000	10000	Females 0	16	80	400	2000	10000
***Spleen**												
*No. of Siderocytes (T)	3/37	0/23	2/19	7/16	18/21	14/16	10/25	6/16	5/11	15/16	7/7	10/10
Lymphoid Hyperplasia (D)	5/20	3/10	3/11	1/10	3/11	2/10	4/18	2/8	3/10	3/11	1/11	1/11
" " (T)	14/37	4/23	3/19	4/16	0/21	1/16	5/25	4/16	0/11	4/16	0/7	2/10
***Liver**												
*Hepatocyte Enlargement (D)	9/20	5/10	7/11	4/10	7/11	9/10	1/18	0/8	2/10	2/11	4/11	5/11
* " " (T)	15/37	3/23	3/19	7/16	16/21	13/16	6/25	1/16	2/11	4/16	2/7	7/10
*Extramedullary Haemopoiesis (D)	0/20	0/10	0/11	2/10	0/11	1/10	0/18	0/8	0/10	0/11	0/11	0/11
*Extramedullary Haemopoiesis (T)	4/37	1/23	0/19	2/16	11/21	12/16	6/25	4/16	1/11	3/16	2/7	1/10
Hepatic Leucocytosis (D)	0/20	0/10	0/11	0/10	0/11	0/10	0/18	0/8	0/10	0/11	2/11	0/11
" " (T)	2/37	2/23	1/19	0/16	1/21	0/16	0/25	0/16	0/11	0/16	0/7	0/10
Hepatocytic Necrosis and Inflammation (D)	0/20	0/10	0/11	0/10	0/11	0/10	0/18	2/8	0/10	0/11	2/11	0/11
Hepatocytic Necrosis and Inflammation (T)	3/37	1/23	3/19	0/16	0/11	0/16	0/25	1/16	0/11	0/16	1/7	0/10
*Congested/Dilated Contrilobular Sinusoids (D)	0/20	0/10	0/11	0/10	0/11	3/10	0/18	1/8	0/10	1/11	1/11	1/11
*Congested/Dilated Contrilobular Sinusoids (T)	0/37	0/23	0/19	2/16	8/21	6/16	1/25	0/16	0/11	0/16	0/7	2/10
*Brown Pigmented Kupffer Cells (T)	0/20	0/10	0/11	0/10	0/11	1/10	0/18	1/8	0/10	0/11	3/11	1/11
*Brown Pigmented Kupffer Cells (T)	0/37	0/23	0/19	0/16	1/21	4/16	0/25	0/16	0/11	0/16	1/7	2/10
*Fat Deposition (D)	7/20	10/10	10/11	5/10	4/11	8/10	5/18	2/8	8/10	7/11	9/11	9/11
*" " (T)	20/37	5/23	3/19	6/16	6/21	5/16	4/25	5/16	1/11	6/16	4/7	8/10
Pancrease												
Fat Necrosis (D)	0/20	0/10	0/11	0/10	0/11	0/10	0/0	0/0	0/0	0/0	0/0	0/0
" (T)	1/37	0/23	0/19	0/16	0/21	0/16	0/0	0/0	0/0	0/0	0/0	0/0
Kidneys												
Glomerulonephritis (D)	0/20	0/10	0/11	0/10	0/11	0/10	0/18	0/8	0/10	0/11	1/11	0/11
" (T)	3/37	0/23	1/19	1/16	0/21	1/16	1/25	1/16	0/11	0/16	0/7	0/10
Perivascular Lymphoid Aggregations (D)	0/20	1/10	0/11	0/10	0/11	0/10	0/18	1/8	2/10	1/11	1/11	1/11
Perivascular Lymphoid Aggregations (T)	2/37	1/23	1/19	2/16	2/21	5/16	4/25	3/16	1/11	2/16	1/7	3/10
Cystic Tubules (D)	0/20	0/10	0/11	0/10	0/11	0/10	0/18	0/8	0/10	0/11	0/11	0/11

11. Histopathological Findings to the Nonneoplastic Lesions - Continued

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Dose Levels (ppm)	Males						Females					
	0	16	80	400	2000	10000	0	16	80	400	2000	10000
Kidneys												
Cystic Tubules (T)	0/37	2/23	0/19	0/16	0/16	0/16	0/25	0/16	1/11	0/16	0/7	0/10
Urinary Bladder (D)	0/20	0/10	0/11	0/10	1/10	0/10	0/18	0/8	0/10	0/11	0/11	0/11
" " (T)	1/37	0/23	1/9	0/16	2/21	0/16	0/25	0/16	0/11	0/16	0/7	0/9
Uterus												
Dilated Lumen (D)	0/0	0/0	0/0	0/0	0/0	0/0	2/18	0/8	3/10	1/11	3/11	2/11
" " (T)	0/0	0/0	0/0	0/0	0/0	0/0	1/25	1/16	0/11	0/16	2/7	3/10
Cystic Endometrial Hyperplasia (D)	0/0	0/0	0/0	0/0	0/0	0/0	0/18	0/8	0/10	1/11	1/11	0/11
Cystic Endometrial Hyperplasia (T)	0/0	0/0	0/0	0/0	0/0	0/0	9/25	4/16	2/11	0/16	1/7	1/10
Distended Lumen (D)	0/0	0/0	0/0	0/0	0/0	0/0	0/18	0/8	0/10	0/11	0/11	0/11
" " (T)	0/0	0/0	0/0	0/0	0/0	0/0	6/25	4/16	2/11	5/16	3/7	4/10
Ovaries												
Angiectasis (D)	0/0	0/0	0/0	0/0	0/0	0/0	0/18	0/8	0/10	1/11	0/11	0/11
" (T)	0/0	0/0	0/0	0/0	0/0	0/0	0/25	1/16	1/11	2/16	1/7	1/10
Prostate												
Prostatitis (D)	0/20	0/10	0/11	0/10	0/10	0/10	0/0	0/0	0/0	0/0	0/0	0/0
" (T)	0/37	0/23	0/19	1/15	0/21	0/16	0/0	0/0	0/0	0/0	0/0	0/0
Seminal Vesicles												
Distended with Colloid (D)	0/20	1/10	3/11	2/10	1/11	0/10	0/0	0/0	0/0	0/0	0/0	0/0
Distended with Colloid (T)	9/37	11/23	7/19	4/15	8/21	4/16	0/0	0/0	0/0	0/0	0/0	0/0
Testes												
Spermatoceles (D)	1/20	0/10	0/11	0/10	1/11	0/10	0/0	0/0	0/0	0/0	0/0	0/0
" (T)	6/37	5/23	3/19	1/16	2/21	5/16	0/0	0/0	0/0	0/0	0/0	0/0
Reduced Spermatogenesis (D)	0/20	0/10	0/11	0/10	0/11	1/10	0/0	0/0	0/0	0/0	0/0	0/0
Reduced Spermatogenesis (T)	7/37	7/23	2/19	1/16	5/21	4/16	0/0	0/0	0/0	0/0	0/0	0/0
Atrophic Seminiferous Tubules (D)	2/20	0/10	0/11	0/10	0/11	0/10	0/0	0/0	0/0	0/0	0/0	0/0
Atrophic Seminiferous Tubules (T)	7/37	4/23	2/19	1/16	4/21	3/16	0/0	0/0	0/0	0/0	0/0	0/0
Thyroids												
Cystic Follicles (D)	0/19	0/10	0/11	0/10	0/11	0/10	0/18	0/8	0/10	0/11	0/11	0/11
" " (T)	0/37	0/22	1/19	0/16	1/21	0/16	0/25	1/16	2/11	0/16	0/7	0/10

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11. Histopathological Findings to the Nonneoplastic Lesions - Continued

Dose Levels (ppm)	Males 0	16	80	400	2000	10000	Females 0	16	80	400	2000	10000
Adrenals												
Medullary Hyperplasia (D)	0/20	0/10	0/10	0/10	0/10	0/10	0/18	0/8	0/10	0/11	0/11	0/10
" " (T)	0/37	1/23	0/19	1/16	0/21	2/16	0/24	0/16	0/11	0/16	0/11	0/10
Prominent Ceroid Cells (D)	1/20	0/10	1/11	0/10	1/11	0/10	1/18	0/8	0/10	0/11	0/11	0/11
Prominent Ceroid Cells (T)	5/37	4/23	2/19	3/16	4/21	3/16	11/24	4/16	1/11	2/16	2/7	4/10
Pituitary												
Pituitary Cysts (D)	0/20	0/10	1/11	0/10	0/11	0/10	0/0	0/0	0/0	0/0	0/0	0/0
" " (T)	0/37	1/22	1/19	1/15	0/19	1/15	0/0	0/0	0/0	0/0	0/0	0/0
Stomach												
Epithelial Hyperplasia (ng) (D)	4/20	1/10	2/11	1/10	0/11	1/10	3/18	2/8	2/10	4/11	2/11	0/11
Epithelial Hyperplasia (ng) (T)	0/37	0/23	0/19	0/16	0/21	0/16	0/25	0/16	0/11	0/16	0/7	0/10
Acanthosis (D)	0/20	1/10	0/11	0/10	0/11	0/10	0/18	0/8	0/10	1/11	0/11	1/11
Acanthosis (T)	1/37	1/23	1/19	1/16	0/21	6/16	4/25	0/16	0/11	3/16	0/7	3/10
Adenomatous Hyperplasia (g) (D)	1/20	1/10	0/11	1/10	0/11	1/10	1/18	0/8	0/10	0/11	0/11	0/11
Adenomatous Hyperplasia (g) (T)	3/37	2/23	1/19	2/16	2/21	0/16	1/25	1/16	1/11	0/16	2/7	0/10
Eyes												
Lenticular Fibre Degeneration (D)	0/20	0/10	0/11	0/10	0/11	0/10	0/0	0/0	0/0	0/0	0/0	0/0
Lenticular Fibre Degeneration (T)	1/37	2/23	2/19	0/16	1/21	1/16	0/0	0/0	0/0	0/0	0/0	0/0
Keratitis (D)	0/0	0/0	0/0	0/0	0/0	0/0	1/18	0/8	1/10	0/11	1/11	0/11
" (T)	0/0	0/0	0/0	0/0	0/0	0/0	1/25	0/16	0/11	1/16	0/7	2/10
Skin												
Ulcers (D)	0/1	0/1	0/0	0/0	0/1	1/1	0/0	0/0	0/0	0/0	0/0	0/0
" (T)	0/0	1/1	0/1	0/0	1/2	0/0	0/0	0/0	0/0	0/0	0/0	0/0

* Noticeable increase of incidence rate (%); (D) - Interim kill after 52 weeks of treatment; (T) - Terminal kill.

11. Histopathological Findings to the Nonneoplastic Lesions - Continued

Summary of Nonneoplastic Findings:

The following treatment-related nonneoplastic changes from the treated mice at the spordic deaths and terminal sacrifices were summarized:

	Males						Females					
Dose Levels (ppm)	0	16	80	400	2000	10000	0	16	80	400	2000	10000
Lung												
*Chronic Pneumonitis	11/104	6/51	10*/52	10*/52	13*/52	13*/52	18/104	7/52	8/52	4/52	2/52	7/51
	11%	12%	19%	19%	25%	25%	17%	13%	15%	8%	4%	14%
Spleen												
*Extramedullary Haemopoiesis	27/104	7/52	15/21	21*/52	19*/52	22*/52	37/104	18/52	19/52	19/52	25*/52	25*/52
	26%	14%	29%	40%	37%	42%	36%	35%	37%	37%	48%	48%
*Sideroctyes	5/104	1/52	2/52	16*/52	32*/52	30*/52	15/104	6/52	13*/52	30*/52	31*/52	43*/52
	5%	2%	4%	31%	62%	58%	14%	12%	25%	58%	59%	83%
Liver												
*Hepatocyte Enlargement	36/104	12/52	11/52	23*/52	35*/52	31*/52	15/104	4/52	5/52	11/52	15*/52	29*/52
	35%	23%	21%	44%	67%	57%	14%	8%	10%	21%	29%	56%
*Extramedullary Haemopoiesis	4/104	3/52	0/52	3/52	12*/52	15*/52	8/104	4/52	2/52	5/52	2/52	5/52
	4%	6%	0	6%	23%	29%	8%	8%	4%	10%	4%	10%
*Hepatocyte Vacuolation	22/104	17/52	9/52	12/52	18*/52	26*/52	33/104	17/52	17/52	17/52	12/52	26*/52
	21%	33%	17%	35%	50%	32%	33%	33%	33%	33%	23%	50%
*Congested/Dilated Contrilobular Sinusoids	0/104	0/52	0/52	2*/52	8*/52	6*/52	1/104	0/52	0/52	0/52	0/52	2*/52
	0	0	0	4%	16%	12%	1%	0	0	0	0	4%
*Brown Pigmented Kupffer Cells	0/104	0/52	1/52	1/52	3*/52	11*/52	1/104	0/52	1/52	0/52	4*/52	11*/52
	0	0	2%	2%	6%	21%	1%	0	2%	0	8%	21%
*Fat Deposition	36/104	18/52	10/52	10/52	13/52	16/52	24/104	9/52	7/52	16/52	12/52	21*/52
	35%	35%	19%	19%	25%	31%	23%	17%	13%	31%	23%	40%

* Significantly treatment-related increase of incidence.

Evaluation and Conclusions:

1. There were no obvious treatment-related effects on mortality, body weights, and food consumption in male and female mice fed Diflubenzuron in the diet during the course of the study.

2. The blue/gray discoloration of the extremitis and dark eyes were persistently observed in male and female mice treated with Diflubenzuron throughout the entire study period. Such abnormal clinical signs of cyanosis were apparently caused by the significantly dose-related elevation of methemoglobin and sulfhemoglobin levels in the treated mice of both sexes during the course of the study (1-91 weeks). These results were also correlated well with the abnormal hematology values noted in the increased mean corpuscular hemoglobin concentration, mean corpuscular hemoglobin value and Heinz bodies from the same treated groups. The presence of increased amounts of methemoglobin and sulfhemoglobin in blood can result in an impairment of oxygen transport with consequent peripheral hypoxia and other cardiac effects. The symptoms in such cases are due seondarily to damage the central nervous system and/or the heart, and the organs most sensitive to oxygen lack. Therefore, the no-effect-level of Diflubenzuron for methemoglobinemia and sulfhemoglobinemia in male and female mice must be clearly established in this study.

3. Treatment-related histomorphologic lesions were observed in the spleen, skin, livers and lungs of treated mice of both sexes. The increased incidences of splenic enlargement, and enlarged livers were detected among Diflubenzuron-treated mice of both sexes at 2000 and 10000 ppm. These results were correlated well with the significant increases of incidence in the higher spleen and liver weights of the same treated groups. The high incidences of congested lungs were also detected in the treated males receiving 2000 and 10000 ppm Diflubenzuron with no effect of treatment on female at the terminal kill. There appears to be some correlation in the increase of incidence rate betwen the congested lungs and the inflammation of the lungs (chronic pneumonitis) from the treated male groups.

4. The significantly treatment-related nonneoplasitic lesions (chronic pneumonitis in the lung, extramedullary haemopoiesis and siderocytes in the spleen, hepatocyte enlargement, hepatocyte vacuolation, extramedullary haemopoiesis, congested/dilated contrilobular sinusoids, brown pigmented Kupffer cells, and fat deposition in the liver) in the treated mice of both sexes were shown in the summarized results No. 11. These results produce evidence of definite histological effects in the spleens, livers, and lungs of orally dosed mice. However, the increased incidences of angiectasis in the ovaries, medullary hyperplasia and prominent ceroid cells in the adrenals, and acanthosis in the stomach found in the treated animals cannot be evaluated properly without the historical control data of the CFLP mice. No other nonneoplastic lesions in a variety of organ tissues from treated mice of both sexse were considered to be significantly different from the control groups.

5. Neoplastic lesions were sporadically distributed among the treated and untreated mice and are summarized in the results No. 10. No neoplastic lesions in a variety of organ tissues from treated mice of both sexes were considered to be significantly different from the control groups. These results produce no evidence of carcinogenicity of Diflubenzuron in the treated CFLP mice at the dose levels tested (16 through 10000 ppm).

6. Classification of Data:

This study is adequate to be rated core guideline for oncogenic potential. However, the studies in chronic feeding and nonneoplastic effects are judged inadequate to be acceptable. Until the reporting deficiencies cited in our conclusion #2 and #4 (e.g., No effect level for methemoglobin and sulfhemoglobin in treated mice was not determined, and all historical control data were missing for the increased incidencies of angiectasis in the ovaries, medullary hyperplasia and prominent ceroid cells in the adrenals, and acanthosis in the stomach of treated mice) are clarified and resolved, these studies remain to be rated supplementary and cannot be upgraded to core (minimum or guideline).