



83-1 A chronic rodent
83-2 A Onco - rodent

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

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Dicofol: Review of a chronic feeding/oncogenicity study
in rats

Caswell No. 93
EPA ID No. 707-203
MRID No. 411500-01

HED Proj. No. 9-1873
EPA Record No. 249,112

TO: D. Edwards, PM (12)
Registration Division (H7505C)

FROM: Whang Phang, Ph.D. *Whang Phang 4/24/90*
Pharmacologist
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THROUGH: K. Clark Swentzel, Section Head *K. Clark Swentzel 4/24/90*
and
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Branch Chief
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The registrant, Rohm & Haas Co., submitted a combined chronic feeding/oncogenicity study in rats. This study has been evaluated. The data evaluation report is attached, and the conclusion is as follows:

Groups of CRL:CD^R BR rats (60/sex/dose) were fed dicofol at dietary concentrations of 0, 5, 50, and 250 ppm for 24 months. The interim sacrifices were carried out at 3, 12, 18, and 24 months with additional groups of 10 rats/sex/dose. The results indicated that dicofol at 250 ppm produced a decrease in body weights of both male and female rats and a slight reduction in food consumption in female rats.

There was a decrease in the levels of triglyceride in 250 ppm males and females. The HMFO activity was increased in 50 and 250 ppm males and females, but a change in the liver microsomal protein concentration was not detected in any group of the treated animals relative to the controls. The latter finding was consistent with

the finding of no compound-related changes in the absolute liver weights.

Gross pathology findings showed an increase in the incidence of prominent architecture of the liver in 50 ppm females and 250 ppm males and females at the 3-month interim sacrifice. At the 12- and 18-month interim sacrifice no compound-related gross pathological changes were reported. At terminal sacrifice, an increase in the incidence of focal discoloration of the liver was seen in 250 ppm females.

Histopathological changes in the liver of 50 and 250 ppm males and females and in the adrenal glands of 250 ppm females were consistently seen at all interim sacrifices and at the termination of the study. The microscopic changes in the liver were characterized by minimal to moderate hypertrophy of centrilobular hepatocytes which was also accompanied by an increased amount of centrilobular, diffuse, or midzonal hepatocellular vacuolation. In some rats necrosis of single hepatocytes or multiple foci of hepatocytes were seen. In the adrenal glands, diffuse vacuolation of cortical cells was often seen. An increase in tumor incidence was not seen in the any group of the treated animals relative to the controls. Based upon the results presented in this study, the LEL for chronic toxicity was 50 ppm; NOEL, 5 ppm.

) This study is classified as minimum, and satisfies the data requirements for the combined study of chronic feeding/oncogenicity testing of dicofol in rats (Guidelines 83-1 and 83-2).

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DATA EVALUATION REPORT

Chemical: Dicofol; Kelthane^R MF Miticide; 4-chloro-alpha-(4-chlorophenyl)-alpha-(trichloromethyl)benzenemethanol

Study Type: 24-Month dietary chronic/oncogenicity study in rats

Caswell No.:	93	HED Proj. No.:	9-1873
MRID No.:	411500-01	EPA ID No.:	707-203
EPA Record No.:	249112		

Sponsor: Rohm and Haas Co.

Testing Laboratory: Rohm and Haas Co.
Toxicology Department
727 Norristown Rd.
Spring House, PA 19477

Citation: Hazelton, GA and Harris, J.C. Dicofol (Kelthane^R MF miticide): 24-Month dietary chronic/oncogenic study in rats. Rohm & Haas; Report No.: 86R-190; March 29, 1989.

Conclusion: Groups of CRL:CD^R BR rats (60/sex/dose) were fed dicofol at dietary concentrations of 0, 5, 50, and 250 ppm for 24 months. The interim sacrifices were carried out at 3, 12, 18, and 24 months with additional groups of 10 rats/sex/dose. The results indicated that dicofol at 250 ppm produced a decrease in body weights of both male and female rats and a slight reduction in food consumption in female rats.

There was a decrease in the levels of triglyceride in 250 ppm males and females. The HMFO activity was increased in 50 and 250 ppm males and females, but a change in the liver microsomal protein concentration was not detected in any group of the treated animals relative to the controls. The latter finding was consistent with the finding of no compound-related changes in the absolute liver weights.

Gross pathology findings showed an increase in the incidence of prominent architecture of the liver in 50 ppm females and 250 ppm males and females at the 3-month interim sacrifice. At the 12- and 18-month interim sacrifices no compound-related gross pathological changes were reported. At terminal sacrifice, an increase in the incidence of focal discoloration of the liver was seen in 250 ppm females.

Histopathological changes in the liver of 50 and 250 ppm males and females and in the adrenal glands of 250 ppm females were consistently seen at all interim sacrifices and at the termination of the study. The microscopic changes in the liver were characterized by minimal to moderate hypertrophy of centrilobular hepatocytes which was also accompanied by an increased amount of centrilobular, diffuse, or midzonal hepatocellular vacuolation. In some rats necrosis of single hepatocytes or multiple foci of hepatocytes were seen. In the adrenal glands, diffuse vacuolation of cortical cells was often seen. An increase in tumor incidence was not seen in the any group of the treated animals relative to the controls. Based upon the results presented in this study, the LEL for chronic toxicity was 50 ppm; NOEL, 5 ppm.

This study is classified as minimum, and satisfies the data requirements for the combined study of chronic feeding/oncogenicity testing of dicofol in rats (Guidelines 83-1 and 83-2).

Materials and Methods

Test article: dicofol (technical) was a brown solid containing 93.3% active ingredient and less than 0.1% DDT-related impurities. The test sample was indentified as Toxicology Department sample number (TD No. 85-211), and lot No. RS-4503.

Animals: Three week old CRL:CD^R BR rats were obtained rom Charles River Lab., Kingston, NY. The test animals were acclimated to the laboratory environment for 3 weeks. During the testing period, each animal was housed individually.

Study Design

All rats received a physical examination 1 week prior to the initiation of the study. The animals which were in poor health were excluded from the test and removed from the testing rooms. The healthy animals were randomly assigned to the following test groups:

Groups	Dicofol ppm	Total No. of Rats		Interim Sac. (No/sex)			
		Male	Female	3	5+	12	18
1	0	100	100	10	10	10	10
2	5	100	100	10	10	10	10
3	50	100	100	10	10	10	10
4	250	100	100	10	10	10	10

+: After 3 months of dosing groups of animals (10 rats/sex/dose) were removed from the treatment diet and fed control diets for 3 months. These groups of animals were called the recovery groups.

months. These groups of animals were called the recovery groups which were inserted into the study to "determine whether thyroid effects, if present at 3 months, were reversible after 3 months of recovery". The report mentioned that at 3 months, the thyroid findings such as serum T³, T⁴ and TSH concentrations and thyroid histopathology did not show any treatment-related changes in the structure or function of the thyroid gland. In light of the lack of the thyroid gland alterations, the animals in these recovery groups were sacrificed after 2 months of recovery time. Gross examination was conducted on each of these animals. Selected tissues such as adrenals, kidneys, liver, thyroid gland, and any gross lesions seen in any tissues from these animals were saved in 10% buffered formalin. However, organ weights were not measured.

In addition, groups of rats (25/sex) were set aside as the sentinel animals to monitor intercurrent disease and the health effects of the rats, and they were housed in the same study rooms as the test animals. At the initiation of the study, 5 rats/sex underwent diagnostic evaluations for virus, mycoplasma serology, respiratory and enteric cultures, exo- and endo-parasite examinations, and major organ histopathology. At 6, 12, and 18 months, blood samples from 12 rats/sex (3/sex/study room) were taken for mycoplasma serology and virus. At the termination of the study, 3 rats/sex/study room were sent for diagnostic evaluations. The remaining animals were sacrificed and discarded.

The report showed that the results from the gross and microscopic examinations of the sentinel rats showed similar morphological findings as those occurred spontaneously in the control and dicofol treatment groups. "No murine pathology in the bacterial, Mycoplasma, protozoan, viral helminth or arthropod groups were isolated or otherwise detected".

Test diet preparation

Dicofol was heated to approximately 65°C until it melted, and the liquid was then stirred and divided into aliquots large enough for each week's test diet preparation. At each week's diet preparation, the aliquots of dicofol were again liquified and stirred to ensure homogeneity. Appropriate amounts of dicofol were weighed and, dissolved in acetone (30 ml) and mixed with approximately 1 kg of feed for 15 minutes to evaporate acetone. This premix was blended with additional feed to obtain the intended concentrations of the test diet. The control diet was prepared in a similar manner. The test diets were prepared weekly.

Samples of freshly prepared diets were taken for analysis of homogeneity. For the stability of the test chemical in the diet, a portion of the prepared diet was placed into a cup and left on top of a cage rack in the study room for a week. At the end of the week, these samples were frozen and later analyzed for stability.

of the test compound during the feeding period and for verification of the targeted concentrations.

Animal observations

Each animal was observed daily for signs of toxicity and mortality during the first 14 weeks of dosing. After 14 weeks, the animals were observed once every two weeks. During the observation, every animal was palpated for external masses. The urine and feces were observed for any abnormalities.

Food consumption and body weight

Both body weights and food consumptions were measured one week prior to the initiation of the study. For first 14 weeks of treatment period, both parameters were determined weekly, and subsequently they were measured at 2 week interval. The values of the compound intake and food efficiency were calculated with the following formula:

$$\text{Compound intake} = \frac{\text{dietary conc. (ppm)} \times \text{food consumption (g/rat/day)}}{\text{body weight (g) at the end of the week}}$$

$$\text{Food efficiency} = \frac{\text{change in group mean body weight}}{\text{group mean food consumption}}$$

It should be noted that food efficiency was calculated for the first 13 weeks of the study which corresponded to the growing period of the test animals, and it was not calculated for the remainder of the study since both food consumption and body weight were measured every other week.

Clinical chemistry

Blood samples were collected from groups of fasted animals (10 rats/sex/dose) for hematology and clinical chemistry evaluations after 3, 6, 12, 18, and 24 months of treatment. The following hematology and clinical chemistry parameters were examined:

Hematology

hematocrit (HCT)	erythrocytes counts & morphology*
hemoglobin	white blood cell (WBC) counts
platelet counts	(total and differential)*
mean corpuscular volume (MCV)	mean corpuscular hemoglobin (MCH)
Mean corpuscular hemoglobin concentration	

(MCHC)

* Erythrocyte counts and morphology and differential WBC counts were conducted only on animals of high dose and the control groups at 3, 6, and 12 months.

Clinical Chemistry

glucose (gluc)	serum urea nitrogen (BUN)
serum glutamic pyruvic transaminase (SGPT)	serum glutamic oxalacetic transaminase (SGOT)
alkaline phosphatase (Alk)	total protein (T. Prot.)
cholesterol (Chol)	albumin (Alb)
globulin (Glob)	A/G ratio
creatinine	total bilirubin (T. Bili)
triglycerides (Trig)	calcium (CA)
phosphorus	gamma glutamyl transferase (GGT)

Urinalysis

Samples of urine were collected from 10 rats/sex in control and the high dose groups after 2, 5, and 11 months of treatment. After 17 and 23 months of treatments, urine samples were also collected from 10 rats/sex/dose in Groups 1, 2, 3, and 4 animals. The following parameters were analyzed:

specific gravity	pH
protein	glucose
ketones	bilirubin
occult blood	appearance (color, clarity)
microscopic sediment	

Thyroid function

The concentrations of serum T_3 , T_4 , and TSH were measured on blood samples collected from 10 rats/sex/dose after 3 months of treatment. The concentrations were determined by radioimmunoassay methods.

Corticosterone determination

The serum corticosterone levels were determined on the blood samples of 10 rats/sex/dose after 2, 5, 11, 17, and 23 months of treatment.

Ophthalmology

All test animals given an eye examination prior to the initiation of the study, and at 12 and 24 months of treatment all rats in groups 1 and 4 were examined.

Hepatic mixed function oxidase (MFO) activity

At 3 and 12 month necropsy times, sections of livers from 5 rats/sex/dose were collected and assayed for MFO activity. The animals used in this assay were randomly selected from each group.

Gross pathology

At end of 3, 12, and 18 months of dosing, 10 rats/sex/dose were sacrificed, and the surviving animals were sacrificed after 24 months treatment. All organs, tissues, and body cavities of each animal which was sacrificed as scheduled, died, or sacrificed moribund were examined grossly. The following organs were weighed at the following times of gross examination:

Organs weighed	Month of Gross Examination			
	3	12	18	24
adrenals	x*	x	x	x
brain		x		x
gonads		x		x
heart		x		x
kidneys	x	x	x	x
liver	x	x	x	x
pituitary		x		
spleen		x		x
thyroid/parathyroid	x*	x*		

*: weighed post fixation

x: organs weighed

Histopathology

The following tissues from all rats were collected and fixed in 10% buffered formalin during the scheduled sacrifice, killed moribund, or found dead:

adrenal+	mammary gland+
aorta+	vagina
bone with bone marrow+	skeletal muscle
brain+	peripheral nerve
epididymides+	pancreas
esophagus+	pituitary
eye+	prostate/vesicular gland
gall bladder	salivary gland
gonads	seminal vesicles+
gross lesions+	skin+
spinal cord+	heart+
spleen+	intestine (colon, cecum,
kidneys*+	duodenum, rectum, ileum, &

stomach+	jejunum)+
trachea+	thymus+
thyroid/parathyroid*	liver**
urinary bladder+	uterus+
vagina	lungs+
lymph node (mesenteric)+	

-
- *: At 3 and 18 months necropsy periods, the sections of the these tissues from 10 rats/sex/dose were microscopically examined.
 - +: At 12 and 24 months necropsy intervals, these tissues from 10 rats/sex from Groups 1 and 4 rats including those which did not survive to the scheduled 12 or 24 months necropsy periods.

In addition, selected tissues such as adrenals, kidneys, liver, lung, thyroid/parathyroid, and other tissues with gross changes from 10 rats/sex/dose of groups 2 and 3 were examined microscopically.

Statistical analysis: The details of statistical methods used in analyzing the results of this study were excerpted from the report and presented in Attachment 1.

Compliance: Signed statement of quality assurance for GLP's was included in the report.

Results

Test article analysis: The report has a Compound Identification Sheet which described the structure, chemical properties, and color of the compound. In addition, this document also presented the information on the batch number and when the chemical was received by the testing laboratory.

Test diet analysis: The data on the diet analysis were excerpted from the report (page 3089) and presented in Table 1. The data demonstrated that the test compound was stable in the diet for 9 days when stored at room temperature, and the preparative procedures provided relatively homogeneous mixtures of the test article in the diet. In addition, the actual concentrations and the targeted concentrations were relatively closed.

Clinical observations: The summarized data on clinical observations did not indicate any treatment-related clinical signs throughout the entire study.

Mortality: The mortality results were selectively excerpted from the report (pages 58-63) and presented as follows:

Weeks in test	Cumulative Mortality*					
	Males			Females		
	52	78	105	53	78	105
0 ppm	5	17	41	3	13	36
5 ppm	5	13	51	1	16	49
50 ppm	4	15	49	1	9	37
250 ppm	4	10	44	2	5	22

*: Each dose group (excluding the interim sacrifice animals) consisted of 60 rats/sex at the initiation of the study.

The data indicated that the survival rates of the treated animals were better than those of the controls at 52 and 78 weeks. Towards the end of the study, the mortality rates increased in the 5 ppm males and females relative to the controls, but this increase was not compound-related. Based upon the individual animal histopathology data, the death of these rats could not be attributed to any single cause. In contrast, few rats in the 50 and 250 ppm female groups died throughout the study.

Body weights: The mean body weights of test animals at various periods of the study were tabulated from the data presented in the Appendix 3 of the report (pages 183-322).

Weeks	Mean Body Weights (gm)							
	Males				Females			
	-1	52	78	104	-1	52	78	104
0 ppm	210 ± 11	762 ± 89	833 ±126	823 ±152	159 ± 9	457 ± 71	513 ± 96	586 ±130
5 ppm	206 ± 11	772 ± 99	804 ±163	782 ±153	158 ± 9	453 ± 71	511 ±101	549 ±124
50 ppm	207 ± 12	739 ± 95	792 ±144	749 ±121	159 ± 9	445 ± 76	518 ±112	527 ±124
250 ppm	206 ± 14	712* ± 85	761 ±122	704 ±106	158 ± 9	354* ± 56	399* ± 86	420* ±107

*: Significantly different from the controls (p<0.05)

The mean body weights in 250 ppm males and females were markedly decreased relative to those of the controls throughout the treatment periods. Relative to the controls, the decrease in body weight towards the end of the study was approximately 15% and 28% in male and females, respectively. The Compound-related effects on body weight was not consistently found in 5 and 50 ppm animals.

Food consumption: The mean food consumption data were excerpted

from the report (pages 75-78) and tabulated as follows:

Mean Food Consumption (gm/animal/day)						
Weeks	Males			Females		
	52	78	104	52	78	104
0 ppm	26.4	30.4	26.5	20.1	24.1	22.0
5 ppm	27.9*	29.3	25.6	20.7	23.3	20.5
50 ppm	27.7	30.4	27.0	20.5	22.5	18.8
250 ppm	26.6	29.1	25.2	17.7*	20.0*	19.3

*: Significantly different from the controls (p<0.05)

The calculated daily food consumption was comparable among the animals of the control, 5, and 50 ppm groups. There was a slight drop in food consumption in 250 ppm females, and sometimes this decrease showed statistical significance.

Food efficiency values were calculated for all dose groups for the first 13 weeks of the study. The results were comparable between treated and control animals.

Compound intake: The values of mean compound intake over the 24 months were excerpted from the report and presented below:

Nominal Dietary Concentration (ppm)	Mean Compound Intake in 24 months (mg/kg/day)	
	Males	Females
5	0.22	0.27
50	2.23	2.69
250	11.34	14.26

Hematology: The hematological values were comparable between the treated animals and the controls. Although there were changes in some of the parameters, the changes were sporadic and small. In addition, the changes did not show any dose-related response.

Clinical chemistry: Besides the changes in the levels of triglyceride in both sexes of 250 ppm animals, no other treatment-related alterations were reported for parameters examined in any dose groups. The changes in triglyceride were excerpted from the report (pages 100-120) and presented in the following table:

Triglyceride Levels At Various Times of the Study (mg/dl)					
Month	3	6	12	18	24
<u>Males</u>					
0 ppm	111± 51	152± 87	179±130	118± 44	235±345

250 ppm	49± 18*	96± 57	168±102	105± 63	201±312
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Females

0 ppm	46± 23	91± 39	225±142	261±294	380±412
250 ppm	37± 10	60± 21	71± 27*	98±100	115± 50

 *: Significantly different from the controls (p<0.05)

It should be noted that in 250 ppm males the drop in triglyceride was more marked at the first 12 months of the study whereas in females the marked decrease occurred at or after 12 months in the study.

Thyroid hormone measurements: At 3 months in the study, the test article did not appear to alter the mean thyroid hormone levels and the TSH concentrations in the serum of the treated animals relative to the controls (Table 2).

Corticosterone concentrations: The corticosterone determinations of the treated animals and those of the controls were comparable. Although there were sporadic differences between the treated animals and the controls, the differences were not statistically significant and the values varied widely.

Analysis of hepatic mixed function oxidase (HMFO) activity: The HMFO activity was significantly increased in 50 and 250 ppm males and females measured as per mg of microsomal protein, per gm of liver, or per total liver (Table 3). This increase was seen in the 3 month as well as the 12 month necropsy, and it was dose-related. The test article, however, did not affect the microsomal protein concentration of the treated animals.

Urinalysis: Some sporadic changes in the parameters of urinalysis were found, but these changes did not show any dose-related response or nor did they persist for any length of time at any dose group.

Ophthalmology: The eye examinations at 12 and 24 months did not reveal any compound related response in Group 4 animals relative to the controls. Only Group 4 and the control animals were examined.

Sacrifice

- A. Gross pathology: The 3-months interim sacrifice revealed an increase in the incidence of gross changes in the liver described as prominent architecture as shown in Table 4. At the terminal sacrifice, an increase in the incidence of focal discoloration of the liver was also seen in 250 ppm females relative to the controls (controls, 17/59; 5 ppm, 16/61; 50 ppm, 24/60; 250 ppm, 34/59). At 12- and 18-month interim sacrifices, no compound-related gross pathological changes

were reported.

- B. Organ weights: There were slight changes in certain absolute organ weights which included liver and thyroid in 250 ppm males and females, but these changes were not statistically significant and were not dose-related. Relative to the controls, there was a statistically significant increase in the ratios of liver weight : body weight in 250 ppm males and females at different examination periods, but this increase was secondary to the body weight decrease in these animals.

C. Histopathology

1). Nonneoplastic changes

The relevant data of non-neoplastic findings were excerpted from the report, and presented in Tables 5A, 5B, 5C, and 5D.

At 3-month interim sacrifice, histopathologic changes were seen in the liver of 50 and 250 ppm males and females and in the adrenal glands of 250 ppm females (Table 5A). The microscopic change in the adrenal glands was characterized by diffuse vacuolation of the cortical cell. In the liver, the changes consisted of minimal to moderate hypertrophy of centrilobular hepatocytes, associated with which was centrilobular/midzonal and diffuse distribution of vacuolation (Table 5A). In 50 and 250 ppm male rats, single cell or multifocal hepatocytic necrosis was associated with hypertrophy. Also the incidence of hepatocellular hypertrophy and the severity of this changes showed a dose-related response in the treated animals.

At 12-month interim sacrifice, the treatment-related microscopic changes were seen in the liver of 50 and 250 ppm males and females, and in the adrenal glands of 250 ppm females (Table 5B). The morphological characteristics of these changes were similar to those described for the 3-month animals.

At 18-month interim sacrifice, compound-related microscopic findings were seen in the liver of 50 and 250 ppm males and females and in the adrenal glands of 1 male and 9 females of 250 ppm groups (Table 5C). The morphological changes were essentially similar to those described for the 3-month animals. It should be noted that although the incidence of diffuse vacuolation of the adrenal was found in only one 250 ppm male, the morphological alterations were similar to those in females of the same dose group.

At the termination of the study (24-month), treatment-related microscopic alterations, which were similar to

in the liver of 50 and 250 ppm male and female rats and in the adrenal glands of 250 ppm males and females (Table 5D). In addition, an increase in the incidence of chronic cystitis of the urinary bladder was seen in 250 ppm females (control, 0/59; 250 ppm, 5/59),

B. Neoplastic lesions

No increase in the tumor incidence of any tissues was found in 3-month and 12-interim sacrifice animals. At 18 and 24 months, certain tumor incidence was observed in some animals of the control and the compound treated groups, but these findings were low and could not be considered as treatment-related response.

Discussion

Groups of CRL:CD^R BR rats (60/sex/dose) were fed dicofol at dietary concentrations of 0, 5, 50, and 250 ppm for 24 months. The interim sacrifices were carried out at 3, 12, 18, and 24 months with additional groups of 10 rats/sex/dose. The results indicated that dicofol at 250 ppm produced a decrease in body weights of both male and female rats and a slight reduction in food consumption in female rats. Compound-related effects on mortality, clinical signs, food efficiency, hematological parameters, thyroid hormone levels, corticosterone levels, urinalysis parameter, and the eye were not seen in the treated animals. The absolute organ weights were comparable between treated and control animals. A slight increase in the ratios of liver weight to body weight was found in the 250 ppm males and females, but this increase was secondary to the drop in the body weights of these animals.

There was a decrease in the levels of triglyceride in 250 ppm males and females. The HMFO activity was increased in 50 and 250 ppm males and females, but a change in the liver microsomal protein concentration was not detected in any group of the treated animals relative to the controls. The latter finding was consistent with the finding of no compound-related changes in the absolute liver weights.

Gross pathology findings showed an increase in the incidence of prominent architecture of the liver in 50 ppm females and 250 ppm males and females at the 3-month interim sacrifice. At the 12- and 18-month interim sacrifices no compound-related gross pathological changes were reported. At terminal sacrifice, an increase in the incidence of focal discoloration of the liver was seen in 250 ppm females.

Histopathological changes in the liver of 50 and 250 ppm males and females and in the adrenal glands of 250 ppm females were

consistently seen at all interim sacrifices and at the termination of the study. The microscopic changes in the liver were characterized by minimal to moderate hypertrophy of centrilobular hepatocytes which was also accompanied by an increased amount of centrilobular, diffuse, or midzonal hepatocellular vacuolation. In some rats necrosis of single hepatocytes or multiple foci of hepatocytes were seen. In the adrenal glands, diffuse vacuolation of cortical cells was often seen. An increase in tumor incidence was not seen in the any group of the treated animals relative to the controls.

The decrease in the body weights and the histopathology findings appeared to indicate that the test animals received adequate dosages in this study. Based upon the results presented in this report, the LEL for chronic toxicity was 50 ppm; NOEL, 5 ppm.

This study is classified as minimum, and satisfies the data requirements for the combined study of chronic feeding/oncogenicity testing of dicofol in rats (Guidelines 83-1 and 83-2).