6/22/00

014649

DATA EVALUATION RECORD

MESOTRIONE (ZA1296)

Study Type: §83-2(b) Oncogenicity Study in Mice

Work Assignment No. 2-01-52X (MRID 44505028)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
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Arlington, VA 22202

Prepared by
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Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

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DATA EVALUATION RECORD

STUDY TYPE: Oncogenicity Study in Mice
OPPTS Number: 870.4200 OPP Guideline Number: §83-2b
DP BARCODE: D259369 SUBMISSION CODE: S541375
P.C. CODE: 122990 TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): Mesotrione (ZA1296) (96.8% a.i.)

SYNONYMS: ZA1296; 2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione; 2-(4-mesyl-2-nitrobenzoyl)-cyclohexane-1,3-dione

CITATION: Rattray, N.J. (1997) ZA1296: 80 Week Carcinogenicity Study in Mice. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Laboratory Report No. CTL/P/5281, November 5, 1997. MRID 44505028. Unpublished.

SPONSOR: Zeneca Agricultural Products, Wilmington, DE

EXECUTIVE SUMMARY: In a mouse oncogenicity study (MRID 44505028), mesotrione (96.8% a.i., Lot/Batch # P17) was administered in the diet to C57BL/10J,CD-1 Alpk mice (55/sex/group) for up to 80 weeks at 0, 10, 350, or 7000 ppm (equivalent to 0/0, 1.4/1.8, 49.7/63.5, and 897.7/1102.9 mg/kg/day [M/F], respectively). The high-dose animals received 3500 ppm of mesotrione for the first 7 weeks of the study and then received 7000 ppm for the remainder of the dosing interval.

The doses were selected on the basis of a 90-day feeding study in mouse carried out in the performing laboratory; no further information was provided. In a subchronic oral toxicity study (MRID 44505022) reviewed with the current submission, mesotrione (96.8% a.i) was administered for 13 weeks to 20 mice/sex/dose at dietary concentrations of 10, 50, 350, or 7000 ppm. All the parameters were unaffected. The NOAEL was 7000 ppm and no LOAEL was observed.

Mortality, clinical signs, food consumption, hematology, organ weights, and macroscopic and histopathological findings for both sexes at all doses were unaffected by treatment with mesotrione. In the 7000 ppm females and in both sexes of the 10 and 350 ppm dose groups, body weights, body weight gains, and food efficiency were also unaffected.

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In the 7000 ppm males, slight, but consistent mean body weight reductions (↓2-9%; $p<0.05$ or 0.01) were observed during weeks 13 to 81. Overall (weeks 1 to 81) body weight gain (calculated by the reviewers) was reduced by approximately 20% compared to controls. Mean food consumption was consistently increased (↑4-10%; $p<0.01$) compared to controls during the first 12 weeks of the study and generally similar to controls thereafter, but food efficiency was reduced ($p<0.05$ or 0.01) during weeks 1-4 (↓12%), 9-12 (↓40%), and overall (weeks 1-12; ↓16%).

The LOAEL is 7000 ppm (equivalent to 897.7/1102.9 mg/kg/day M/F) based on minimal but, consistently reduced body weights, and reduced body weight gains and food efficiency in males. The NOAEL is 350 ppm (equivalent to 49.7/63.5 mg/kg/day M/F).

In this study no treatment-related neoplastic changes were observed.

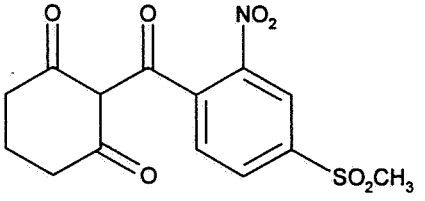
The submitted study is classified as **acceptable/guideline (§83-2b)** and does satisfy the guideline requirements for a carcinogenicity study in mice.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Mesotrione (ZA1296)
   Description: Light beige solid
   Lot/Batch #: P17
   Purity (w/w): 96.8% a.i.
   Stability of compound: The test substance was stable in the diet for up to 16 days stored at room temperature and up to 40 days stored at -20°C
   CAS #: 104206-82-8
   Structure:



2. Vehicle: Diet

3. Test animals: Species: Mouse
   Strain: C57BL/10J$_f$CD-1 Alpk
   Age at start of dosing and mean weight at week 1: Approximately 5-7 weeks old; 21.4-21.5 g (males), 17.6-17.9 g (females)
   Source: Barriered Animal Breeding Unit, Zeneca Pharmaceuticals, Alderley Park
   Housing: Five/cage in mouse cages suitable for this strain
   Diet: CT1 (Special Diet Services, Ltd., Essex, UK), ad libitum
   Water: Tap water, ad libitum

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Environmental conditions:
Temperature: 21±2°C
Humidity: 55±15%
Air changes: At least 15/hour
Photoperiod: 12 hours light/12 hours dark
Acclimation period: Approximately 14 days

B. STUDY DESIGN:

1. In life dates: start: 02/14/95 end: 09/06/96

2. Animal assignment: The rats were randomly assigned (stratified by weight) to the test groups shown in Table 1.

Table 1. Study design [a]

Test Group	Dietary Concentration (ppm)	Mean Achieved Dose (mg/kg/day)[c]		Number of Animals	
		Males	Females	Males	Females
Control	0	0	0	55	55
Low	10	1.4	1.8	55	55
Mid	350	49.7	63.5	55	55
High	3,500/,7000 [b]	897.7	1,102.9	55	55

a) Data obtained from the study report, page 18.
b) High-dose animals received 3500 ppm test compound for the first 7 weeks of the study and then received 7000 ppm for the remainder of the dosing interval
c) Achieved doses obtained from pp 23 MRID 44505028, and Appendix F, pages 218 and 219.

3. Dose selection rationale - The doses chosen for the current study were based on the results of a 90-day feeding study in the C57BL/10J$_f$CD-1 Alpk mouse carried out in the performing laboratory; no further information was provided. In a subchronic oral toxicity study (MRID 44505022) reviewed with the current submission, mesotrione (96.8% a.i.; Batch No. P17) was administered for 13 weeks to 20 C57BL/10J$_f$CD-1 mice/sex/dose at dietary concentrations of 10, 50, 350, or 7000 ppm (equivalent to 1.7, 8.4, 61.5, and 1212.4 mg/kg/day in males and 2.4, 12.4, 80.1, and 1537.1 mg/kg/day in females). Two control groups of 20 C57BL/10J$_f$CD-1 mice/sex (40/sex) were fed untreated diet during the study. Mortality, clinical observations, body weight, body weight gain, food consumption and utilization, ophthalmoscopic observations, clinical chemistry parameters, organ weights, and gross and microscopic pathological findings were unaffected by the test substance. Hematology parameters did not appear to be affected by the test substance. The NOAEL for this study is 7000 ppm (equivalent to 1212.4/1537.1 mg/kg/day [M/F]). The LOAEL was not observed.

4. Dose preparation, administration, and analysis - The appropriate amount of test substance was mixed with the diet to obtain a premix and the premix was diluted with additional food to obtain the appropriate dose. Homogeneity (top, middle, bottom) was determined by analyzing samples from the 10, 3500, and 7000 ppm dose formulations. Stability was determined at concentrations of 1 and 7000 ppm over a period of up to 16 days at room temperature and up to 40 days at -20°C. Concentration analyses were performed on all dose preparations from samples collected every two months throughout the study.

   Results:
   Homogeneity (range as mean.% of nominal): 93.7-125%
   Stability (range as mean % of day 0):
   84.8% on day 16 stored at room temperature
   90.5% on day 40 stored at -20°C
   Concentration (range as mean % of nominal): 91.7-130%
   The analytical data indicated that the mixing procedure was adequate and that the variation between nominal and actual dosage to the study animals was acceptable.

5. Statistics - Body weights, food consumption, food utilization, hematology, and organ weight data were evaluated by analysis of variance and/or covariance followed by Student's t-test. Kaplan-Meier survival estimates were calculated for each sex and treatment group. Intergroup comparisons of mortality and an overall test for trend were performed using a logrank test. Tumor incidence were analyzed using Fisher's exact test and a test for trend was performed using the Cochran-Armitage Test.

C. METHODS:

1. Observations - Changes in clinical condition or behavior were recorded daily. Detailed clinical observations were recorded weekly.

2. Body weight - All animals were weighed weekly up to week 12, then every two weeks until study termination. Body weights were also recorded at scheduled termination.

3. Food consumption and efficiency - Food consumption (g/mouse/day) for each cage was determined weekly for weeks 1-12 and then every fourth week until study termination. Food utilization was calculated as the body weight gained per cage/100 g food consumed.

4. Water consumption - Water consumption was not measured.

5. Ophthalmoscopic examination - Ophthalmoscopic examinations were not performed.

6. Blood analyses - During week 53, blood was collected via the tail vein from all surviving animals and a blood smear was prepared. At scheduled termination, all surviving animals were bled by cardiac puncture and the checked (X) parameters below were examined:

a. Hematology:

X	Hematocrit (HCT)	X	Leukocyte differential count
X	Hemoglobin (HGB)	X	Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)	X	Mean corpusc. HGB conc.(MCHC)
	Corrected leukocyte count (Cor WBC)	X	Mean corpusc. volume (MCV)
X	Erythrocyte count (RBC)		Reticulocyte count
X	Platelet count		Cell morphology
	Blood clotting measurements	X	Erythrocyte distribution width
	(Prothrombin time)	X	Examination of a blood film
	(Activated partial thromboplastin time)		

7. Sacrifice and Pathology - At study termination (week 80), all surviving animals were anaesthetized, exsanguinated, and subjected to a gross pathological examination. The following checked (X) tissues were collected from all animals sacrificed at scheduled termination, animals that died prematurely, and animals sacrificed *in extremis* and all tissues (except for the oral and nasopharyngeal cavities) were examined microscopically. Additionally, the (XX) organs were weighed.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
	Tongue	X	Aorta	XX	Brain
X	Salivary glands	X	Heart	X	Periph. nerve
X	Esophagus	X	Bone marrow	X	Spinal cord (3 levels)
X	Stomach	X	Lymph nodes	X	Pituitary
X	Duodenum	X	Spleen	X	Eyes
X	Jejunum	X	Thymus		
X	Ileum				GLANDULAR
X	Cecum		UROGENITAL	XX	Adrenal gland
X	Colon	XX	Kidneys		Lacrimal gland
X	Rectum	X	Urinary bladder	X	Mammary gland
XX	Liver	XX	Testes	X	Parathyroids
X	Pancreas	X	Epididymides	X	Thyroids
X	Gall bladder	X	Prostate		
		X	Seminal vesicle		OTHER
	RESPIRATORY	X	Ovaries and Oviducts	X	Bone
X	Trachea	X	Uterus	X	Skeletal muscle
X	Lung	X	Cervix	X	Skin
	Nose			X	All gross lesions and masses
	Pharynx			X	Preputial gland
	Larynx			X	Harderian gland
				X	Nasopharyngeal cavity
				X	Oral cavity

II. RESULTS

A. Observations:

1. Toxicity - No treatment-related clinical signs were observed.

2. Mortality - No differences in Kaplan-Meier Survival estimates were observed in either sex of the treated groups throughout the study when compared to the respective control groups. Percentage survival in all dose groups of mice at 80 weeks was approximately 78-89%. Mortalities in male and female mice at termination are shown below.

Mortalities in mice fed mesotrione for 80 weeks [a]

Sex	0 ppm	10 ppm	350 ppm	7,000 ppm
Males	7 (12.7%)	9 (16.4%)	8 (14.6%)	8 (14.6%)
Females	6 (10.9%)	12 (21.8%)	6 (10.9%)	12 (21.8%)

a) Date taken from pp. 23, MRID 44505028

B. Body weight:

All mean body weight data were adjusted by the sponsor for initial weight. Slight, but consistent mean body weight reductions (↓2-9%; $p<0.05$ or 0.01) were observed in the 7000 ppm males during weeks 13 to 81 (Table 2). Overall body weight gain (calculated by the reviewers) in the high-dose males was reduced by approximately 20% compared to controls. In the 7000 ppm females, body weights were only minimally, but consistently reduced (↓2-4%; $p<0.05$ or 0.01) during weeks 35 to 67. Body weights in the other dose groups were similar to control values.

Table 2. Mean body weights (g) at selected intervals in mice fed mesotrione for 80 weeks.[a]

Week	Dietary levels (ppm)			
	0	10	350	7000
Males				
1	21.4	21.4	21.5	21.5
13	28.9	28.6	28.7	28.0**(↓ 3%)
15	29.3	29.2	29.2	28.7*(↓ 2%)
49	34.9	34.8	33.6**(↓ 4%)	31.9**(↓ 9%)
53	34.7	34.8	33.7*(↓ 3%)	32.1**(↓ 7%)
57	35.2	35.2	34.0*(↓ 3%)	32.2**(↓ 9%)
81	34.9	35.3	34.7	32.3**(↓ 7%)
Overall Body Weight Gained	13.5	13.9	13.2	10.8
Females				
1	17.6	17.9	17.7	17.6
10	23.3	23.6	23.7*(↑ 2%)	23.5
35	27.1	26.9	27.2	26.2**(↓ 3%)
39	27.4	27.3	27.8	26.8*(↓ 2%)
53	28.2	28.0	28.0	27.4*(↓ 3%)
55	28.3	28.0	28.2	27.2**(↓ 4%)
67	28.9	29.0	29.1	28.1*(↓ 3%)
81	29.6	29.4	29.7	29.0
Overall Body Weight Gained	12.0	11.5	12.0	11.4

a. data obtained from Table 7, pages 73-84 - MRID 44505028.
* or ** Significantly different from controls $p<0.05$ or 0.01, respectively.

C. Food consumption and efficiency:

Mean food consumption of high-dose males was consistently increased (↑4-10%; $p<0.01$) compared to controls during the first 12 weeks of the study (Table 3a) and generally similar to controls thereafter. Sporadic differences ($p<0.05$ or 0.01) in food consumption were observed in the 10 and 350 ppm males and all of the female dose groups.

Food efficiency was reduced ($p<0.05$ or 0.01) in the high-dose males during weeks 1-4

(↓12%), 9-12 (↓40%), and overall (weeks 1-12; ↓16%) (Table 3b). Sporadic differences ($p<0.05$ or 0.01) in food efficiency were observed in the 10 and 350 ppm males; all female dose groups were similar to controls throughout the first 12 study weeks.

Table 3a. Mean food consumption (g/mouse/day) at selected intervals in mice fed mesotrione for up to 80 weeks.[a]

Week	1 ppm	10 ppm	350 ppm	7,000 ppm
Males				
1	4.5	4.5	4.6	4.7**(↑ 4%)
8	4.1	4.2	4.4**(↑ 7%)	4.5**(↑ 10%)
12	4.3	4.3	4.4	4.5**(↑ 5%)
52	4.2	4.1	4.2	4.2
48	4.3	4.2	4.1*(↓ 5%)	4.1
80	3.7	3.9	3.8	3.7
Females				
1	4.6	4.7	4.7	4.5
8	4.6	4.8*(↑4%)	4.8*(↑ 4%)	4.8*(↑ 4%)
24	4.1	4.4	4.3	4.5*(↑ 10%)
52	4.1	4.2	4.1	4.1
68	4.2	4.5*(↑7%)	4.2	4.4
80	3.8	4.1	4.2*(↑ 11%)	4.0

a Data obtained from pages 85-90 - MRID 44505028.
* or ** Significantly different from controls $p<0.05$ or 0.01, respectively.

Table 3b. Food efficiency (g growth/100 g food) in male mice exposed to mesotrione for up to 80 weeks. [a]

Weeks	Dietary levels (ppm)			
	0	10	350	7000
1-4	3.33	3.00*(↓ 10%)	3.18	2.94*(↓ 12%)
5-8	1.64	1.89*(↑ 15%)	1.84	1.54
9-12	1.28	1.16	0.90**(↓ 30%)	0.77**(↓ 40%)
1-12	2.10	2.03	1.98	1.76**(↓ 16%)

a Data obtained from page 91- MRID 44505028.
* or ** Significantly different from controls $p<0.05$ or 0.01, respectively.

E. Blood analyses:

1. Hematology - No treatment-related differences from concurrent controls were observed in the blood smears obtained at week 53 nor in any hematological parameter. Decreases (↓43-94%; $p<0.05$ or 0.01) in white cell, lymphocyte, eosinophil, basophil, and large unclassified cell counts were observed in the 10, 350, and 7000 ppm females; these findings were not dose-related and may have been related to exceptionally high values obtained from two control animals (429 and 439). Tables 4a and 4b showing selected hematology findings are presented with and without two control outlier animals. These data showed that where these high white cell count values were excluded from the analysis then there were no differences between the control and treatment groups. Only minor differences (<6%) from controls in hemoglobin, hematocrit, red blood cell count, and mean cell volume were observed in the 350 and 7000 ppm males.

Table 4a. Selected hematology findings ($x10^9$/L) in female mice exposed to mesotrione for up to 80 weeks. [a]

Cell type	Dietary levels (ppm)			
	0	10	350	7000
White blood cell	6.53	3.22*(↓ 51%)	3.58*(↓ 45%)	3.74*(↓ 43%)
Lymphocyte	5.20	1.99*(↓ 62%)	2.49*(↓ 52%)	2.58*(↓ 50%)
Eosinophil	0.283	0.052*(↓ 82%)	0.061*(↓ 78%)	0.064*(↓ 77%)
Basophil	0.233	0.015	0.014*(↓ 94%)	0.016*(↓ 93%)
Large unclassified	0.376	0.123*(↓ 67%)	0.124*(↓ 67%)	0.103**(↓ 73%)

a Data obtained from Table 10, page 95 - MRID 44505028.
* or ** Significantly different from controls $p<0.05$ or 0.01, respectively.

Table 4b. Selected hematology findings ($x10^9$/L) in female mice (excluding control females 421 and 439) exposed to mesotrione for up to 80 weeks. [a]

Cell type	Dietary levels (ppm)			
	0	10	350	7000
White blood cell	3.32	3.22	3.58	3.74
Lymphocyte	2.28	1.99	2.49	2.58
Eosinophil	0.073	0.052	0.061	0.064
Basophil	0.012	0.015	0.014	0.016
Large unclassified	0.167	0.123	0.124	0.103

a Data obtained from Table 10, page 96 - MRID 44505028.
* or ** Significantly different from controls $p<0.05$ or 0.01, respectively.

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G. Sacrifice and pathology:

1. Organ weights - No treatment-related differences were observed in organ weights. The following differences ($p<0.05$ or 0.01) from controls were considered not to be treatment-related because they were minor, and/or there were no corroborating histopathological or gross pathological data: In the 350 ppm females - absolute and adjusted (for body weight) adrenal glands (↑25% each); in the 7000 ppm females-absolute and adjusted brain weights (↓2% each); in the 350 and 7000 ppm females-absolute and adjusted kidney weights (↑7-10%); and in the 350 and 7000 ppm males-adjusted liver weights (↑5-8%).

2. Gross pathology - There were no macroscopic findings of toxicological concern.

3. Microscopic pathology:

   a) Non-neoplastic: When all animals were combined, including all animals that died and those sacrificed on schedule, an increased incidence (# animals/55) of minimal to moderate eosinophilic change in the gall bladder was detected in the 350 and 7000 ppm females (16 and 21/55 treated, respectively, vs 7/55 controls) (Table 5). There were no other treatment-related findings of the gall bladder or liver in the 350 and 7000 ppm females and this finding is, therefore, considered to be of doubtful toxicological significance.

   In the 10, 350, and 7000 ppm males, there was an increase in the incidence (# animals/55) of minimal to moderate salivary gland atrophy (4, 5, 9, respectively, vs 1 control) and in splenic lymphoid proliferation (2, 4, 8, respectively, vs 1 control). The reviewers agree with the sponsor that the increased incidence of salivary gland atrophy is unlikely to be treatment-related; the incidences in the 10 and 350 ppm males were within the historical control range (5/55) and the incidence in the high-dose males is considered of equivocal toxicological concern. The incidence of splenic lymphoid proliferation is also considered to be not treatment-related; the incidences in the 10 and 350 ppm males were within the historical control range (4/55) and no increased incidence of lymphosarcoma was observed.

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Table 5. Incidence (# of animals) of selected microscopic findings in mice dosed with mesotrione for up to 80 weeks. [a]

Observation	Dietary Level (ppm)				Historical controls[b]
	0	10	350	7000	
	Males				
Salivary gland- Atrophy					
minimal	0	2	0	5	
slight	1	1	3	2	
moderate	0	1	2	2	
Total	1	4	5	9	5/55
Spleen- Lymphoid proliferation					
minimal	0	0	0	1	
slight	1	1	3	5	
moderate	0	1	1	2	
Total	1	2	4	8	4/55
	Females				
Gall bladder-Eosinophilic change					
minimal	1	3	6	9	
slight	5	1	8	8	
moderate	1	0	2	4	
marked	0	1	0	0	
Total	7	5	16	21	–

a Data obtained from Table 14, page 171, 182 and 185; n=55 - MRID 44505028
b Data obtained from page 220 - MRID 44505028
– No historical data was provided

b) Neoplastic: No treatment-related neoplastic changes were observed.

III. DISCUSSION

A. Investigators conclusions - Treatment with mesotrione for up to 80 weeks at dose levels of up to 7000 ppm produced no evidence of carcinogenicity in mice of both sexes.

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B. Reviewer's discussion/conclusions - In a mouse oncogenicity study (MRID 44505028), mesotrione (96.8% a.i., Lot/Batch # P17) was administered in the diet to C57BL/10J$_f$CD-1 Alpk mice (55/sex/group) for up to 80 weeks at 0, 10, 350, or 7000 ppm (equivalent to 0/0, 1.4/1.8, 49.7/63.5, and 897.7/1102.9 mg/kg/day [M/F], respectively). The high-dose animals received 3500 ppm of mesotrione for the first 7 weeks of the study and then received 7000 ppm for the remainder of the dosing interval. Dietary analyses at select study intervals confirmed that nominal diet concentrations of mesotrione were achieved.

Mortality, clinical signs, hematology, organ weights, and macroscopic findings for both sexes at all doses were unaffected by treatment with mesotrione.

Slight, but consistent mean body weight reductions (↓2-9%; $p<0.05$ or 0.01) were observed in the 7000 ppm males during weeks 13 to 81. Overall body weight gain (calculated by the reviewers) in the high-dose males was reduced by approximately 20% compared to controls. In the 7000 ppm females, body weights were only minimally, but consistently reduced (↓2-4%; $p<0.05$ or 0.01) during weeks 35 to 67. Body weights in the other dose groups were similar to control values.

Mean food consumption of high-dose males was consistently increased (↑4-10%; $p<0.01$) compared to controls during the first 12 weeks of the study and generally similar to controls thereafter. Sporadic differences ($p<0.05$ or 0.01) in food consumption were observed in the 10 and 350 ppm males and all of the female dose groups. The differences in food consumption in the high-dose males is not considered adverse.

Food efficiency was reduced ($p<0.05$ or 0.01) in the high-dose males during weeks 1-4 (↓12%), 9-12 (↓40%), and overall (weeks 1-12; ↓16%). Sporadic differences ($p<0.05$ or 0.01) in food efficiency were observed in the 10 and 350 ppm males; all female dose groups were similar to controls throughout the first 12 study weeks.

An increased incidence (# animals/55) of minimal to moderate eosinophilic change in the gall bladder was detected in the 350 and 7000 ppm females (16 and 21/55 treated, respectively, vs 7/55 controls) was considered to be of doubtful toxicological significance. The minimal to moderate salivary gland atrophy and splenic lymphoid proliferation observed in all treated males were considered of equivocal toxicological concern.

The LOAEL is 7000 ppm (equivalent to 897.7/1102.9 mg/kg/day M/F) based on minimal but, consistently reduced body weights, and reduced body weight gains and food efficiency in males. The NOAEL is 350 ppm (equivalent to 49.7/63.5 mg/kg/day M/F).

No treatment-related neoplastic changes were observed in this study.

The submitted study is classified as **acceptable/guideline (83-2b)** and does satisfy the guideline requirements for a carcinogenicity study in mice.

C. Study deficiencies -None noted.

D. Note: Copies of neoplastic data; Table 15, 16 and 17, pages 192-199 (MRID 44505028) are attached and are not available electronically.

THE FOLLOWING ATTACHMENTS ARE NOT AVAILABLE ELECTRONICALLY. SEE THE FILE COPY.

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Pages 16 through 23 are not included in this copy.

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