DATA EVALUATION RECORD

7/19/2000

MESOTRIONE (ZA1296)

Study Type: §82-1(a), 90 Day Feeding Study in Rats

Work Assignment No. 2-01-52Q (MRID 44505020)

Prepared for
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Office of Pesticide Programs
U.S. Environmental Protection Agency
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DATA EVALUATION RECORD

STUDY TYPE: Subchronic Oral Toxicity feeding - rats
OPPTS Number: 870.3100

OPP Guideline Number: §82-1a

DP BARCODE: D259369
P.C. CODE: 122990

SUBMISSION CODE: S541375
TOX. CHEM. NO.: None

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

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

CITATION: Pinto, P.J. (1997) ZA1296: 90 Day Dietary Toxicity Study in Rats. Central Toxicology Laboratory, Cheshire, UK. Laboratory Report No. CTL/P/4986, November 5, 1997. MRID 44505020. Unpublished.

SPONSOR: Zeneca Ag Products, Wilmington, DE

EXECUTIVE SUMMARY: In this subchronic oral toxicity study (MRID 44505020), mesotrione (96.8% a.i., Lot/batch # P17) was administered for 90 days to 12 Alpk:AP$_f$SD rats/sex/dose at dietary concentrations of 0, 2.5, 5.0, 7.5, or 150 ppm (equivalent to [M/F] 0/0, 0.21/0.23, 0.41/0.47, 0.63/0.71, or 12.46/14.48 mg/kg/day, respectively).

No treatment-related findings were observed in the 2.5 or 5.0 ppm groups. No mortalities occurred during the study. Body weights (adjusted for week 1 body weight), body weight gains, food consumption and utilization, hematology, clinical chemistry, and urinalysis parameters, and organ weights were unaffected by the test substance.

Cloudy eyes were observed during the clinical examinations during weeks 8-14 in the 7.5 ppm males and during weeks 7-14 in the 150 ppm males. In the 150 ppm females, cloudy eyes were observed during week 12 only. During the ophthalmoscopic examination at week 13, slight to marked hazy opacity, slight to moderate opacity, and vascularization were observed in the 7.5 and 150 ppm males. Slight opacity was observed in the 150 ppm females and 5 ppm males. In addition, plaque opacity of the lens was observed in the 150 ppm females. Eye opacity was observed in the 7.5 and 150 ppm males during the gross pathological examination. In addition, slight to moderate keratitis of the eye was observed in the 7.5 and 150 ppm males and in the 150

ppm females during the histopathological examination. Histopathological abnormalities of the kidney included minimal to slight unilateral hydronephrosis and minimal chronic progressive glomerulonephropathy in the 150 ppm males.

The LOAEL for this study is 7.5 ppm (equivalent to 0.63 mg/kg/day for males, 0.71 mg/kg/day for females) based upon corneal lesions in males. The NOAEL is 5 ppm (equivalent to 0.41 mg/kg/day for males, 0.47 mg/kg/day for females).

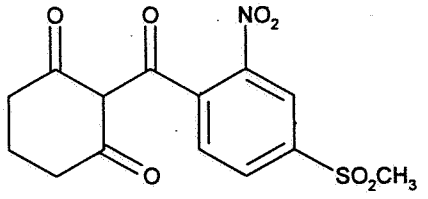
The submitted study is classified as **acceptable/guideline (§82-1a)** and satisfies the requirements for a subchronic oral toxicity study in rats.

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 (WTC 15213-17-1)
   Purity (w/w): 96.8% a.i.
   Stability of compound: The test substance was stable for over 2 years when stored at ambient temperatures in the dark.
   CAS #: 104206-82-8
   Structure:



2. Vehicle: Diet

3. Test animals: Species: Rat
   Strain: Alpk:AP$_f$SD
   Age and mean weight at the start of dosing: Approximately 6 weeks old; 170.0-174.1 g (males), 140.5-147.5 g (females)
   Source: Rodent Breeding Unit, Zeneca Pharmaceuticals, Alderley Park, Cheshire, UK
   Housing: Four/cage in cages suitable for strain and weight range
   Diet: CT1 diet (Special Diet Services, Ltd., Essex, UK), ad libitum, except during urine collection
   Water: Tap water, ad libitum, except during urine collection
   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 2 weeks

B. STUDY DESIGN:

1. In life dates: Start: 12/20/95 End: 3/22/96

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

Table 1. Study design

Test Group	Dietary Concentration (ppm)	Achieved Dose [a] (mg/kg/day) [M/F]	Males	Females
Control	0	0/0	12	12
Low	2.5	0.21/0.23	12	12
Mid	5.0	0.41/0.47	12	12
Mid-high	7.5	0.63/0.71	12	12
High	150	12.46/14.48	12	12

a Mean achieved dosages (mg/kg/day) were obtained from the study report Appendix E, page 96.

3. Dose selection rationale - The dose levels selected for this study were based on the results of a previous 90-day feeding study in the Alpk:AP$_f$SD rat in this laboratory; no further information was provided.

4. Diet preparation and analysis - Diets were prepared by mixing the test substance with food to obtain a premix and then further diluting the premix with food to obtain the desired concentrations. The frequency of diet preparations and storage conditions were not provided. Homogeneity was assessed by testing samples (top, middle, bottom) from the 2.5 and 150 ppm dose formulations. Stability of the test substance in the diet was determined in previous studies (PM0983 and PR1001) for 1 and 7000 ppm dose formulations stored at room temperature for 7 days and at -20°C for up to 40 days. Concentration analyses were performed on samples from the 0, 2.5, 5, 7.5, and 150 ppm dose formulations prepared on two separate occasions.

Results -
Homogeneity analysis (range as mean % of nominal): 96-106%

Stability analysis
storage at room temperature (range as mean % of day 0): 84.8-107.4%
storage at -20°C (range as mean % of day 0): 87.5-111.2%

Concentration analysis (range as mean % of nominal): 101-116%

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.

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5. Statistics - Body weight, food consumption and utilization, hematology, clinical chemistry, urinalysis, and organ weight data were evaluated by analysis of variance (ANOVA) and/or covariance followed by Student's t-test.

C. METHODS:

1. Observations - Animals were inspected once daily for mortality and clinical signs of toxicity. Detailed clinical examinations were performed weekly.

2. Body weight - Each animal was weighed weekly throughout the study.

3. Food consumption - Food consumption was measured continuously throughout the study and calculated as a weekly mean for each cage (g/rat/day). Food utilization was calculated as the body weight gained per cage per 100 g food consumed.

4. Water consumption - Water consumption was not reported.

5. Ophthalmoscopic examination - Ophthalmoscopic examinations were performed on all test animals prior to the start of treatment and within one week of study termination.

6. Blood - Upon study termination, blood was collected via cardiac puncture from all rats. The checked (X) hematology and clinical blood chemistry parameters 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)
X	Erythrocyte count (RBC)	X	Mean corpusc. volume (MCV)
X	Platelet count		Reticulocyte count
	Blood clotting measurements	X	Erythrocyte distribution width
	(Thromboplastin time)		
X	(Activated partial thromboplastin time)		
	(Clotting time)		
X	(Prothrombin time)		

b. Clinical Chemistry

	ELECTROLYTES		OTHER
X	Calcium	X	Albumin
X	Chloride	X	Blood creatinine
	Magnesium	X	Blood urea nitrogen
X	Phosphorus	X	Total Cholesterol
X	Potassium		Globulin
X	Sodium	X	Glucose
			Direct bilirubin
	ENZYMES	X	Total bilirubin
X	Alkaline phosphatase (ALK)	X	Total serum protein (TP)
	Cholinesterase (ChE)	X	Triglycerides
X	Creatine phosphokinase		
	Lactic acid dehydrogenase (LDH)		
X	Serum alanine aminotransferase (ALT)		
X	Serum aspartate aminotransferase (AST)		
X	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase		

7. Urinalysis - During the last week of the study, urine was collected from all animals over a 16-18 hour period. During urine collection, rats were housed in metabolism cages and fasted and water deprived. The checked (X) parameters were examined.

X	Appearance	X	Glucose
X	Volume	X	Ketones
X	Specific gravity	X	Bilirubin
X	pH	X	Blood
X	Sediment (microscopic)		Nitrate
X	Protein		Urobilinogen

8. Sacrifice and Pathology - At study termination, all animals were anaesthetized, exsanguinated, and subjected to a gross pathological examination. The following CHECKED (X) tissues were collected from all animals; the tissues (except for the nasal passages and oral cavity) from the control and high-dose animals were examined microscopically. Furthermore, the eyes from the intermediate groups 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	Thyroids w/ parathyroids
X	Pancreas	XX	Epididymides		
		X	Prostate		OTHER
	RESPIRATORY	X	Seminal vesicle	X	Bone (Femur and Sternum)
X	Trachea	X	Ovaries	X	Skeletal muscle
X	Lung	X	Uterus	X	Skin
	Pharynx		Vagina	X	All gross lesions and masses
	Larynx	X	Cervix	X	Harderian gland
				X	Oral cavity
				X	Nasopharyngeal cavity

II. RESULTS

A. Observations

1. Mortality - No mortalities occurred during the study.

2. Clinical signs - Selected clinical signs are presented in Table 2. Cloudy eyes were observed during weeks 8-14 in the 7.5 ppm males (2/12 treated vs. 0/12 controls) and during weeks 7-14 in the 150 ppm males (7/12 treated vs. 0/12 controls). In the 150 ppm females, cloudy eyes were observed during week 12 only (1/12 treated vs. 0/12 controls). No other treatment-related clinical signs of toxicity were observed in any treated group.

Table 2. Selected clinical observations noted in rats treated with mesotrione for 90 days. [a]

Observation	Males					Females				
	Dose (ppm)					Dose (ppm)				
	0	2.5	5.0	7.5	150	0	2.5	5.0	7.5	150
Cloudy eyes	0	0	0	2(12)	7(47)	0	0	0	0	1(1)

a Data obtained from the study report Table 4, pages 45 and 48; n=12. Data presented as number of affected animals. Number of observations is listed parenthetically.

B. Body weight and body weight gain - No treatment-related differences in adjusted (for week 1 body weight) body weights or body weight gains (Table 3) were observed in any treated group relative to concurrent controls. Adjusted body weights were sporadically increased in the males (↑4-7%, p≤0.05 or 0.01) and decreased in the females (↓4-6%, p≤0.05 or 0.01); however, these differences from controls were minor.

Table 3. Overall body weight gains (g) in rats treated with mesotrione for 90 days.[a]

Dose (ppm)				
0	2.5	5.0	7.5	150
Males				
301.2	320.7	315.9	329.6	325.5
Females				
118.8	109	113.4	120.3	108.2

a Overall body weight gains (weeks 1-14) were calculated by the reviewers from information provided in the study report, Table 6 pages 54-57; n=12.

C. Food consumption/utilization and compound intake

1. Food consumption - No treatment-related differences in food consumption were observed in any treated group. Increased food consumption was noted in the 150 ppm males during weeks 2, 3, and 6 (↑4-7%, p≤0.05); however, these increases were minor and not sustained over time. Food consumption was decreased in the 2.5 ppm females during weeks 4, 8, and 13 (↓6-8%, p≤0.05); however, these decreases were minor and not dose-dependent.

2. Food utilization - No treatment-related differences in food utilization were observed in any treated group.

3. Compound intake - The achieved mean dosages are shown in Table 1.

D. Ophthalmoscopic examination - The ophthalmoscopic examination at week 13 revealed the following corneal abnormalities at 150 ppm (data presented as number of occurrences per 24 eyes, Table 4): (i) marked hazy opacity (5/24 males only); (ii) slight opacity (males-1/24, females-5/24); (iii) moderate opacity (2/24 males only); (iv) marked opacity (1/24 males only); and (v) vascularization (8/24 males only). Corneal abnormalities in the 7.5 ppm males included the following: (i) slight hazy opacity (1/24); (ii) slight opacity (3/24); (iii) moderate opacity (3/24); and (iv) vascularization (3/24). The only corneal abnormality noted at 5 ppm

was slight opacity (1/24 males). Slight and moderate hazy opacity was also observed in the control males (1/24 each). In addition, plaque opacity of the lens was observed in the 150 ppm females (2/24 treated vs. 1/24 controls).

Table 4. Ophthalmoscopic observations (# observations/eye) noted in rats treated with mesotrione for 90 days. [a]

Observation	Males					Females				
	Dose (ppm)					Dose (ppm)				
	0	2.5	5.0	7.5	150	0	2.5	5.0	7.5	150
Number of eyes examined	24	24	24	24	24	24	24	24	24	24
Both eyes normal	22	23	23	17	15	23	24	24	24	17
Cornea										
hazy opacity (total)	2	0	0	1	5	0	0	0	0	0
slight	1	0	0	1	0	0	0	0	0	0
moderate	1	0	0	0	0	0	0	0	0	0
marked	0	0	0	0	5	0	0	0	0	0
opacity (total)	0	0	1	6	4	0	0	0	0	5
slight	0	0	1	3	1	0	0	0	0	5
moderate	0	0	0	3	2	0	0	0	0	0
marked	0	0	0	0	1	0	0	0	0	0
vascularized	0	0	0	3	8	0	0	0	0	0
Lens										
plaque opacity	0	0	0	0	0	1	0	0	0	2

a Data obtained from the study report Table 5, pages 51-52.

E. Blood analyses

1. Hematology - No treatment-related differences in hematology parameters were observed in any treated group relative to controls. Large unclassified cells were increased in the 150 ppm males and females (↑33-48%, $p \leq 0.05$); however, the increases were not dose-related. Other differences ($p \leq 0.05$) in hematology parameters which were not dose-dependent, and therefore, unrelated to treatment included the following: (i) increased monocytes in the 5 ppm males and females (↑29-35%) and the 150 ppm males (↑32%); (ii) increased eosinophils in the 2.5 ppm males (↑24%); (iii) decreased activated partial thromboplastin time in the 7.5 ppm males (↓15%); (iv) and decreased platelet counts in the 5 and 150 ppm females (↓10-12%). Minor differences from concurrent controls (↓2-↑7, $p \leq 0.05$ or 0.01) were noted among various treatment groups (except at 7.5 ppm) which included decreased mean cell hemoglobin and mean cell hemoglobin

concentration, and increased hematocrit, mean cell volume, mean cell hemoglobin, and erythrocyte distribution. No other differences in hematology parameters were observed in any treated groups.

2. Clinical chemistry - Selected clinical chemistry parameters are presented in Table 5. Increased alanine aminotransferase and aspartate aminotransferase activities (↑39 and 53%, respectively; p≤0.01) were observed in the 150 ppm males. Although these increases may suggest the possibility of liver damage in these animals, comparable alanine aminotransferase and aspartate aminotransferase activities noted in control animals in a previous subchronic study in which higher doses were administered (MRID 44505019) and unusually large standard deviations associated with the mean activities of these enzymes, which may have been influenced by one outlier animal with extremely high values, imply that the increased values are not biologically relevant. Cholesterol was increased (p≤0.05) in the 7.5 ppm males (↑15%) and 150 ppm females (↑14%), and potassium was increased in the 150 ppm females (↑14%); however, these increases were not dose-dependent, and therefore, considered not to be treatment-related. Alkaline phosphatase was decreased in the 150 ppm males (↓17%, p≤0.01); however, this decrease had no clinical significance. Minor differences from concurrent controls (↓2-↑7, p≤0.05 or 0.01) included increased albumin, increased total protein, decreased sodium, and decreased chloride among various treatment groups in both males and females.

Table 5. Selected clinical chemistry parameters in male rats treated with mesotrione for 90 days.[a]

Parameter	Dose (ppm)				
	0	2.5	5.0	7.5	150
Alanine aminotransferase (IU/L)	68.7±12.5	73.0±20.4	68.7±5.6	65.2±15.5	95.8**±54.8 (↑39)
Aspartate aminotransferase (IU/L)	85.8±11.5	96.3±24.2	87.8±9.3	93.3±16.6	131.3**±90.5(↑53)

a Data obtained from the study report Table 10, page 66; n=12. Percent difference from controls is listed parenthetically.
** Statistically different from controls at p≤0.01.

F. Urinalysis - No treatment-related differences from concurrent controls were observed in any urinalysis parameter. In the 150 ppm males, urine specific gravity was slightly increased (↑1%, p≤0.05) and pH was non dose-dependently decreased (5.83 treated vs. 6.42 controls).

G. Sacrifice and Pathology:

1. Organ weight - Increased absolute liver weights were observed in all treated males (↑14-26%, p≤0.05 or 0.01); in addition, liver weights (adjusted for body weight) were increased in these animals (↑8-18%, p ≤0.05 or 0.01) as well as in the high-dose females

(↑10%, p≤0.01). Since no concomitant liver pathology was observed, the increase in absolute and relative liver weights was probably due to an adaptive response as a result of the administration of the test compound and is not considered adverse at these dosages. Increased absolute kidney weights were observed in the 7.5 and 150 ppm males (↑12% each, p≤0.05). These increases were not dose-dependent and were most likely due to slightly increased body weights in these animals. Minor differences were observed in absolute brain weights (↓4-↑3%, p≤0.01 or 0.05) in treated males and females, but were considered unrelated to treatment.

2. Gross pathology - Eye opacity was observed in the 7.5 (2/12) and 150 (7/12) ppm males (vs. 0/12 controls, Table 6). No other treatment-related gross pathological changes were observed in any treated group.

Table 6. Gross pathological observations (# affected animals) noted in rats treated with mesotrione for 90 days. [a]

Observation	Males					Females				
	Dose (ppm)					Dose (ppm)				
	0	2.5	5.0	7.5	150	0	2.5	5.0	7.5	150
Eye opacity	0	0	0	2	7	0	0	0	0	0

a Data obtained from the study report Table 15, page 81; n=12.

3. Microscopic pathology - Slight keratitis of the eye was observed in both sexes at 150 ppm (males-5/12, females-1/12) and in the 7.5 ppm males (3/12). Moderate keratitis was observed in the 150 (2/12) and 7.5 (1/12) ppm males. Keratitis was not observed in any other treated group or in the controls. The following abnormalities of the kidney were observed in the 150 ppm males: (i) minimal unilateral hydronephrosis (2/12 treated vs. 1/12 controls); (ii) slight unilateral hydronephrosis (1/12 treated vs. 0/12 controls); and (iii) minimal chronic progressive glomerulonephropathy (2/12 treated vs. 0/12 controls).

Table 7. Selected histopathological observations noted in rats treated with mesotrione for 90 days.[a]

Observation	Males					Females				
	Dose (ppm)					Dose (ppm)				
	0	2.5	5.0	7.5	150	0	2.5	5.0	7.5	150
Eye										
Keratitis (total)	0	0	0	4	7	0	0	0	0	1
slight	0	0	0	3	5	0	0	0	0	1
moderate	0	0	0	1	2	0	0	0	0	0
Kidney										
Number examined	12	0	0	0	12	12	0	0	0	12
Unilateral hydronephrosis (total)	1	0	0	0	3	0	0	0	0	0
minimal	1	0	0	0	2	0	0	0	0	0
slight	0	0	0	0	1	0	0	0	0	0
Chronic progressive glomerulonephropathy (total)	0	0	0	0	2	0	0	0	0	0
minimal	0	0	0	0	2	0	0	0	0	0

a Data obtained from the study report Table 16, page 84; n=12.

III. DISCUSSION

A. Investigator's conclusions - The eye was the target organ for toxicity, with corneal opacity observed during the ophthalmoscopic examination and keratitis observed during the histopathological examination. The NOAEL for this study was 5 ppm in the males and 7.5 ppm in the females.

B. Reviewer's discussion - In this subchronic oral toxicity study, mesotrione was administered for 90 days to 12 Alpk:AP$_f$SD rats/sex/dose at dietary concentrations of 0, 2.5, 5.0, 7.5, or 150 ppm (equivalent to [M/F] 0/0, 0.21/0.23, 0.41/0.47, 0.63/0.71, or 12.46/14.48 mg/kg/day, respectively). 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.

No treatment-related findings were observed in the 2.5 or 5.0 ppm groups. No mortalities occurred during the study. Body weights (adjusted for week 1 body weight), body weight gains, food consumption and utilization, hematology, clinical chemistry, and urinalysis parameters, and organ weights were unaffected by the test substance.

During the clinical examinations, cloudy eyes were observed during weeks 8-14 in the 7.5 ppm males (2/12 treated vs. 0/12 controls) and during weeks 7-14 in the 150 ppm males (7/12

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treated vs. 0/12 controls). In the 150 ppm females, cloudy eyes were observed during week 12 only (1/12 treated vs. 0/12 controls).

The ophthalmoscopic examination at week 13 revealed the following corneal abnormalities at 150 ppm (data presented as number of occurrences per 24 eyes): (i) marked hazy opacity (5/24 males only); (ii) slight opacity (males-1/24, females-5/24); (iii) moderate opacity (2/24 males only); (iv) marked opacity (1/24 males only); and (v) vascularization (8/24 males only). Corneal abnormalities in the 7.5 ppm males included the following: (i) slight hazy opacity (1/24); (ii) slight opacity (3/24); (iii) moderate opacity (3/24); and (iv) vascularization (3/24). The only corneal abnormality noted at 5 ppm was slight opacity (1/24 males). Slight and moderate hazy opacity was also observed in the control males (1/24 each). In addition, plaque opacity of the lens was observed in the 150 ppm females (2/24 treated vs. 1/24 controls).

During the gross pathological examination, eye opacity was observed in the 7.5 (2/12) and 150 (7/12) ppm males (vs. 0/12 controls). During the histopathological examination, slight keratitis of the eye was observed in both sexes at 150 ppm (males-5/12, females-1/12), and in the 7.5 ppm males (3/12), and moderate keratitis was observed in the 150 (2/12) and 7.5 (1/12) ppm males. The following histopathological abnormalities of the kidney were observed in the 150 ppm males: (i) minimal unilateral hydronephrosis (2/12 treated vs. 1/12 controls); (ii) slight unilateral hydronephrosis (1/12 treated vs. 0/12 controls); and (iii) minimal chronic progressive glomerulonephropathy (2/12 treated vs. 0/12 controls).

The LOAEL for this study is 7.5 ppm (equivalent to 0.63 mg/kg/day for males, 0.71 mg/kg/day for females) based upon corneal lesions in males. The NOAEL is 5 ppm (equivalent to 0.41 mg/kg/day for males, 0.47 mg/kg/day for females).

The submitted study is classified as **acceptable/guideline (§82-1)** and satisfies the requirements for a subchronic oral toxicity study in rats.

C. Study deficiencies - The following deficiencies were noted, but do not change the conclusions of this review:

- No dose rationale was provided; however an additional subchronic feeding study in the rat (MRID 44505019) was submitted for review.