(10-30-98)

DATA EVALUATION RECORD

AMINE OXIDE

Study Type: 83-5; Combined Chronic/Oncogenicity Study - Rats

Work Assignment No. 3-27 (MRID 44586201)

Prepared for

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DATA EVALUATION RECORD

STUDY TYPE: Combined Chronic/Oncogenicity - Rat
OPPTS Number: 870.4300 OPP Guideline Number: §83-5

DP BARCODE: D247460 SUBMISSION CODE: None
P.C. CODE: 000439 TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): Amine oxide (27% a.i.)

SYNONYMS: P0571, dodecyl dimethyl amine oxide

CITATION: Cardin, C.W., B.E. Domeyer, and L. Bjorkquist. (1983) Toxicological Evaluation of Commercial Alkyldimethylamine Oxides: Two-Year Chronic Feeding and Dermal Studies. International Research and Development Corporation, Mattawan, MI. Study No. IRDC-191-408. April 4, 1983. MRID 44586201. Published in: Fundamental and Applied Toxicology, Vol. 5, pp 869-878; 1985.

SPONSOR: The Proctor & Gamble Company, Cincinnati, Ohio.

EXECUTIVE SUMMARY:

In a chronic toxicity/oncogenicity study (MRID 44586201), amine oxide (27% a.i.) was administered to CD rats (50/sex/dose) in the food at dose levels of 0, 0.01, 0.1, or 0.2% [achieved doses of 0, 4.24/5.23, 42.3/52.6, or 87.4/107 mg/kg/day (M/F)] for 104 weeks. In addition, 10 rats/sex/group were terminated at 52 weeks.

No significant differences were observed in survival rates in either sex of the treated groups throughout the study when compared to the respective control groups. At termination (104 weeks), survival rates ranged from 48%-68% in males and 51%-68% in females. Clinical signs, hematological parameters, clinical chemistry, urinalysis, organ weights, and histopathology were also unaffected by treatment.

Body weights were significantly lower ($p<0.05$-0.001) for high-dose males and females (15-14% vs controls) at 7 of 8 timepoints.

Mean food consumption (g/rat/day) was occasionally significantly decreased in high-dose males (↓5-10% vs controls; 5/8 periods; $p<0.01$ or 0.001) and high-dose females (↓4-7% vs controls; 6/8 periods; $p<0.05$-0.001).

There was an increase in bilateral cataracts/opacities in the high-dose male rats (↑167% vs controls) at final necropsy. During study weeks 66 to 104, the incidence of bilateral cataract/opacities in the high-dose females was 2.4-6.4% vs 0% in the controls. The rats were examined by two different ophthalmologists, both of whom did not attribute any findings to the treatment. However, when compared to the sub-chronic toxicity study (MRID 44475203), in which 12/20 males and 8/20 females had lenticular cataracts/opacities in the 0.4% treatment groups at 13 weeks, it may be possible that a treatment-related effect is being observed.

No differences of toxicological concern were noted at the 0.1 and 0.01% dosages.

The chronic LOEL for this study is 0.2% [87.4/107 (M/F) mg/kg/day] based on decreased body weight and ophthalmological opacities/cataracts. The chronic NOEL is 0.1% [42.3/52.6 (M/F) mg/kg/day].

Under the conditions of this study, amine oxide did not show any signs of oncogenicity it CD rats.

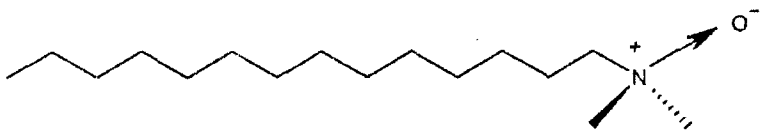
This chronic toxicity/oncogenicity study is classified as **acceptable (§83-5(a))** and satisfies the Subdivision F guideline requirements for a chronic toxicity study (§83-1) and a carcinogenicity study (§83-2) in rats.

COMPLIANCE: Signed and dated Data Confidentiality, GLP, and Quality Assurance statements were provided. A Flagging statement was not provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: Amine Oxide
   Description: Clear, slightly viscous liquid
   Lot/Batch #: Not reported
   Purity: 27% a.i.
   Storage: Under refrigeration, 40±4°F
   CAS #: 70592-80-2
   Structure:



2. Vehicle: Diet

3. Test animals: Species: Rat
   Strain:Charles River CD®
   Age and weight at study initiation: 6 weeks old; 162-222 g (males) and 109-176 g (females)
   Source: Charles River Breeding Laboratories, Inc., Portage, MI
   Housing: Individually in stainless steel hanging wire-mesh cages
   Diet: Ziegler NIH-07 powdered diet, ad libitum
   Water: Tap water, ad libitum
   Environmental conditions:
   Temperature: Approximately 71-75°F
   Humidity: Approximately 46-70%
   Air changes: 12.8-13.3/h
   Photoperiod: 12 h dark/12 h light
   Acclimation period: 14 days

B. STUDY DESIGN:

1. In life dates - start: 6/4/79 end: 6/4/81.

2. Animal assignment: Animals were assigned by a computer generated randomization procedure (weight stratified) to treatment groups as indicated in Table I.

Table 1. Study design

Concentration in Diet (% a.i.)	Dosages Achieved M/F (mg/kg/day)	Number of Animals			
		Main Study 24 months		Interim Sacrifice 12 months	
		Males	Females	Males	Females
0	0	50	50	10	10
0.01	4.24/5.23	50	50	10	10[b]
0.1	42.3/52.6	50	50	10	10
0.2	87.4/107	50	50	10[b]	10

a Data extracted from study report pages 19 and 32.
b Only 9 animals/dose were sacrificed since 1 animal/dose died before 12 month interim sacrifice.

3. Dose selection rationale: In a previously reviewed subchronic toxicity study (MRID 44475203), amine oxide (27.72% a.i.) was administered to Sprague-Dawley rats (20/sex/dose) by feeding at dose levels of 0, 0.1, 0.2, or 0.4% (0, 63, 112, or 236 mg/kg/day for males; 0, 80, 150, or 301 mg/kg/day for females) for 13 weeks.

   In the 0.4% treatment group at 13 weeks, body weight gains of male and female rats were 23-26% lower and alkaline phosphatase activities were 28-60% higher than the controls. In addition, 12/20 males and 8/20 females had lenticular opacities (cataracts). In the 0.2% treatment group at 13 weeks, body weight gains were 8 and 18% lower in males and females, respectively, alkaline phosphatase activities were 45% higher in males, and 3/19 males had cataracts compared to the controls. Reduced food consumption (≤8% during the final 4 weeks) was observed in both the 0.4 and 0.2% treatment groups. No treatment-related deaths occurred during the study. There were no biologically significant differences between rats in the 0.1% treatment group and the controls. There were no treatment-related clinical signs or differences in the hematology, urine, organ weights, or gross or microscopic histology of the treated rats compared to the controls. No neoplastic tissue was observed.

   Based on the results of the sub-chronic study, 0.2% was selected as the high-dose for the subsequent chronic/oncology study. Low- and mid-dose levels chosen were 0.01 and 0.1, respectively.

4. Diet Preparation and Analysis: Diets were prepared weekly with the appropriate amount of test substance added to the rat ration. This premix was added to the remainder of the basal diet and then stored under refrigeration. Treated and control diets were sampled (top, middle, and bottom) weekly throughout the dosing period for

homogeneity/concentration analyses. For stability analyses, samples were exposed to environmental conditions in the animal room for one week and representative samples were collected as described for homogeneity. All samples were shipped frozen for analysis.

Results: Homogeneity/concentration analyses: Mean concentrations of samples containing 0.01, 0.1, and 0.2% of test article were 0.009±0.004, 0.08±0.02, and 0.18±0.02, repectively.

Stability Analyses: No stability data were provided with this submission; however, in a previously reviewed 13 week subchronic oral toxicity study (MRID 44475203) stability analyses were performed in test diets containing 0.1, 0.2, and 0.4% amine oxide stored for up to 12 weeks at 40±4°F. Mean concentrations of samples containing 0.1, 0.2, and 0.4% of test article at week 13 were 0.21%, 0.28%, and 0.44%, repectively.

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the study animals was acceptable.

5. Statistics: Body weights, food consumption and efficiency, hematological and blood chemistry parameters, urinalysis parameters, and absolute and relative organ weights were compared by one-way ANOVA, Barlett's test for homogeneity of variance, and the least significant difference criterion. If Barlett's test was significant, pair-wise comparisions were made using Mann-Whitney U test.

C. METHODS:

1. Observations: Animals were inspected for clinical signs and mortality twice daily. Detailed observations were recorded weekly.

2. Body weight: Weights were recorded weekly for the first 14 weeks, biweekly for the next 12 weeks, and monthly thereafter.

3. Food consumption and compound intake: Weekly mean food consumption values were determined for the first 14 weeks and at week 40 of the study. Weekly mean values were averaged at 2-week intervals for weeks 15-28, and at monthly intervals thereafter. Mean compound consumption and food efficiency were calculated from food consumption and body weight data.

4. Ophthalmoscopic examination: Ophthalmoscopic examinations were performed on each animal prior to treatment and at 3, 6, 12, 16, 19, 22, and 24 months. After diagnosis of dacryoadenitis in some animals at 3 months, randomly selected rats were examined for this disease at weekly intervals.

5. Blood Analyses: Blood was collected from all rats sacificed at 12 and 24 months for hematological and clinical chemistry analyses. Blood samples were obtained via puncture

of the orbital sinus plexus from animals that had been fasted for 16-23 hours. The CHECKED (X) parameters below were examined in each blood sample.

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
	Platelet count		Erythrocyte morphology
	Blood clotting measurements		
	(Thromboplastin time)		
	(Prothrombin time)		

b. Clinical Chemistry:

	ELECTROLYTES		OTHER
	Calcium	X	Albumin
	Chloride		Blood creatinine
	Magnesium	X	Blood urea nitrogen
	Phosphorus		Total Cholesterol
	Potassium	X	Globulins
	Sodium		Glucose
			Total bilirubin
	ENZYMES	X	Total serum protein
	Alkaline phosphatase (AP)		Triglycerides
	Plasma cholinesterase (PL-ChE)		Albumin/globulin ratio
	Erythrocyte cholinesterase (RBC-CHE)		
	Brain cholinesterase (BR-CHE)		
	Creatine phosphokinase		
	Lactate dehydrogenase (LDH)		
X	Serum alanine aminotransferase (ALT)		
X	Serum aspartate aminotransferase (AST)		
	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase (GLDH)		

6. Urinalysis: Urinalyses were performed on all interim 12 month sacrificed rats. The following CHECKED (X) parameters were examined.

	Transparency	X	Glucose
X	Volume	X	Ketones
X	Specific gravity	X	Bilirubin
X	pH	X	Blood
X	Sediment (microscopic)	X	Color
X	Protein	X	Urobilinogen
	Osmolality		Chloride
X	Appearance		Creatinine
			Potassium
			Sodium
			Urea
		X	Nitrites

7. Sacrifice and Pathology: All preselected interim 12-month (10 rats/sex/dose) and terminally sacrificed rats received a gross pathological examination and the CHECKED (X) tissues were collected for histological examination. Additionally, the (XX) organs were weighed.

	DIGESTIVE		CARDIOVASC./HEMAT.		NEUROLOGIC
	Tongue		Aortic arch	XX	Brain
X	Salivary glands	XX	Heart	X	Peripheral nerve
X	Esophagus	X	Bone marrow	X	Spinal cord (thoraco-lumbar)
X	Stomach	X	Lymph nodes	X	Pituitary
X	Duodenum	X	Spleen	X	Eyes
X	Jejunum	X	Thymus		GLANDULAR
X	Ileum		UROGENITAL	X	Adrenal glands
X	Cecum	XX	Kidneys		Harderian gland
X	Colon	X	Urinary bladder	X	Mammary gland
X	Rectum	XX	Testes	X	Parathyroids/thyroid
XX	Liver	X	Epididymis		
	Gall bladder	X	Prostate		OTHER
X	Pancreas	X	Seminal vesicles	X	Bone
	RESPIRATORY	XX	Ovaries	X	Skeletal muscle
X	Trachea	X	Uterus	X	Skin
X	Lungs		Vagina		Lacrimal gland
	Nasal cavity		Ureter		Zymbal gland
	Pharynx		Urethra	X	All gross lesions and masses
X	Larynx			X	Blood smears
				X	Costochondral junction, rib
				X	Bone marrow smears

Tissues from animals in the control and high-dose groups from the interim sacrifice, and all animals at the terminal sacrifice and all that died or were sacrificed *in extremis*, during the

study received a full histopathological examination. Gross lesions were examined from low- and mid-dose animals dying during the study or sacrificed in extremis; organ weights from these animals were not determined.

II. RESULTS

A. Observations

1. Toxicity - The general condition, behavior, and appearance of treated animals was considered unaffected by treatment.

2. Mortality - No significant differences were observed in survival rates in either sex of the treated groups throughout the study when compared to the respective control group. At 104 weeks, the survival rate ranged from 48%-68% in males and 51%-68% in females, which exceeded the guideline requirement (not less than 25%) for this interval.

B. Body weights - Body weights (Table 2) were significantly lower ($p<0.05$-0.001) for males (↓9-14% vs controls) and females (↓5-14% vs controls) in the high-dose treatment group at 7 of 8 timepoints. The reductions at the remaining timepoint (week 39) was within the range of the other reductions (males - ↓11%; females - ↓8%), but were not statistically significant. Mid-dose males had significantly lower body weight at 5 of 8 timepoints (↓3-8% vs controls) and low-dose males had significantly lower body weights at 3 of 8 timepoints (↓5-6% vs controls). However, the reductions in these latter two groups were less than 10%, and consequently are not considered to be of toxicological concern. At termination (104 weeks), only high-dose males and females had signficantly lower body weights (↓12-14% vs controls). Mid- and low-dose female body weights were not signficantly different from controls at any timepoint.

Table 2. Mean body weights (g) of rats during oral (feeding) treatment with amine oxide.[a]

Treatment Week	Treatment Rate (%)			
	0	0.01	0.1	0.2
Males				
1	254	249	248	237
13	546	531	528*	496***
26	611	588	585**	555***
39	685	644	643	607
52	740	694**	687***	656***
65	801	752**	735***	692***
78	808	766*	752*	704**
91	791	772	748	716**
104	795	787	759	697**
Females				
1	172	171	172	167
13	298	298	295	283**
26	330	322	321	308**
39	356	351	347	328
52	384	387	374	349**
65	431	432	416	381**
78	448	459	442	400**
91	458	470	455	406*
104	477	524	460	409*

a Data obtained from Table 1, pages 63 -65, and 67 of the study report.
*, **, or *** - Significantly different from the controls at $p<0.05$, 0.01, or 0.001, respectively.

C. Food consumption and compound intake

1. Food consumption and food utilization - Mean food consumption (g/rat/day; Table 3) was occasionally significantly decreased in low- (↓4-5% vs controls; 2/8 periods; $p<0.001$), mid- (↓3-5% vs controls; 4/8 periods; $p<0.05$-0.001) and high-dose males (↓5-10% vs controls; 5/8 periods; $p<0.01$ or 0.001) and high-dose females (↓4-7% vs controls; 6/8 periods; $p<0.05$-0.001). The reductions in food consumption in the low- and mid-dose

males and females were all less than 10%, and thus, were not considered to be of toxicological concern. There were no significant differences in food utilization between the treated and control groups.

Table 3. Mean food consumption (g/rat/day) of rats during oral (feeding) treatment with amine oxide.[a]

Treatment Week	Treatment Rate (%)			
	0 (Control 2)	0.01	0.1	0.2
Males				
1-13	23.9	23.5	23.1**	22.3***
14-26	23.2	22.8	22.5	22.5
27-39	23.7	22.5***	22.5***	22.2***
40-52	23.4	22.4***	22.2***	22.0***
53-65	24.8	22.8	23.4	22.2**
66-78	25.1	24.4	24.3*	23.8**
79-91	24.5	24.7	24.2	24.0
92-104	23.1	23.8	23.4	22.6
Females				
1-13	16.4	16.4	16.2	15.7*
14-26	15.8	15.8	15.8	15.6
27-39	16.2	16.2	16.1	15.6**
40-52	16.3	16.2	16.2	15.7**
53-65	17.8	17.1	18.0	16.6*
66-78	19.0	19.0	18.6	17.8***
79-91	19.2	18.9	18.7	18.2***
92-104	18.1	19.1	18.0	17.2

a Data obtained from Table 4, pages 71 and 72 in the study report.
*, **, or *** - Significantly different from the controls at $p<0.05$, 0.01, or 0.001.

2. Compound intake - Calculated compound consumption by male rats in the 0.01, 0.1, and 0.2% treatment groups averaged 4.24, 42.3, and 87.4 mg/kg/day, respectively, over the

104-week treatment period. Measured compound consumption by female rats in the 0.01, 0.1, and 0.2% treatment groups averaged 5.23, 52.6, and 107 mg/kg/day, respectively.

D. Ophthalmoscopic examination

There was an increase in bilateral cataracts/opacities in the high-dose male rats (↑167% vs controls) at final necropsy (Table 4). During study weeks 66 to 104, the incidence of bilateral cataract/opacities in the high-dose females was 2.4-6.4% vs 0% in the controls. The rats were examined by two different ophthalmologists, both of whom did not attribute any findings to the treatment. However, when compared to the sub-chronic toxicity study (MRID 44475203), in which 12/20 males and 8/20 females had lenticular cataracts/opacities in the 0.4% treatment groups at 13 weeks, it may be possible that a treatment-related effect is being observed.

Table 4. Incidence (%) of unilateral (bilateral) cataracts and opacities in rats treated with amine oxide for 24 months.

Dose	Week			
	66	80	95	104
Males				
Controls	0 (0)	0 (2.4)	12.5(6.3)	12.5(8.3)
0.01%	2.3 (2.3)	2.4 (7.1)	2.8 (8.3)	6.3 (6.3)
0.1%	2.2 (4.3)	6.7 (0)	20.5 (7.7)	11.8 (8.8)
0.2%	4.1 (8.2)	4.3 (4.3)	10.8 (10.8)	9.4 (21.9)
Females				
Control s	0 (0)	2.1 (0)	14.3 (0)	13.8 (0)
0.01%	2.0 (0)	4.3 (0)	11.1 (0)	11.1 (0)
0.1%	0 (0)	0 (0)	2.6 (0)	0 (0)
0.2%	0 (6.4)	7.1 (2.4)	11.8 (5.9)	17.2 (3.4)

a Data summarized by the reviewers from information in the study report, Appendix P, pages 1308 through 1419.

E. Blood work

1. Hematology - No treatment-related differences in hematological parameters were observed.

2. Clinical Chemistry - A significant, dose-dependent decrease in serum globulin occurred in males at 104 weeks (controls - 4.1 g/dl; low-dose - 3.8 g/dl; mid-dose - 3.7 g/dl, $p<0.01$; high-dose - 3.6 g/dl, $p<0.01$). The decreases were small (↓7-12% vs controls), and are not considered to be of toxicological concern. Serum globulin levels were unaffected in females.

   All other differences in clinical blood chemistry parameters between rats in the treated and control groups did not appear to be treatment-related.

F. Urinalysis

No differences in urine parameters were observed.

G. Sacrifice and Pathology

1. Organ weight - At the interim necropsy (12 months), there were no differences of toxicological concern in absolute or relative organ weights. The high-dose females had increased absolute and relative ovary weights (↑109% vs controls, p = not significant). However, these large increases were due to a single outlier (1.09 g vs mean value of 0.130). Upon exclusion of the outlier, the absolute ovarian weights were increased 16% vs controls. A significant increase in relative liver weight in the high-dose females (↑5% vs controls, $p<0.05$) occurred, but the difference was small and due to a reduction in body weights (↓9% vs controls), and is therefore not of toxicological concern.

   At termination (24 months), there were no differences of toxicological concern in absolute or relative organ weights. High-dose females had increased absolute (↑10% vs controls, p = non significant) and relative (↑28% vs controls, $p<0.05$) ovary weights. Relative brain weights were increased (↑13% vs controls, $p<0.05$) in high-dose males. In high-dose females, increased ($p<0.05$) relative kidney weights (↑9% vs controls) and brain weights (↑15%) were noted. These increases were due to decreased body weights and are therefore not of toxicological concern.

2. Gross pathology - No treatment-related gross postmortem differences were observed between rats in the treated and the control groups at the either the interim or final necropsy. All abnormalities appeared to occur randomly and sporadically in all study groups.

3. Microscopic pathology:

   a) Non-neoplastic and Neoplastic

      I. Interim Necropsy and Final Necropsy - No treatment-related microscopic postmortem differences were observed between rats in the treated and the control groups. All abnormalities appeared to occur randomly and sporadically in all study

groups. Only neoplastic lesions with an incidence of 4 or greater in the high-dose were analyzed for statistical significance.

III. DISCUSSION

A. Investigator's Conclusions - There were no treatment-related clinical signs. Body weights were reduced in treated males at all dose levels; these reductions were frequently statistically significant. At final necropsy, however, only high-dose males were significantly different from controls. In the females, high-dose body weights were different from controls. Food consumption followed a similar pattern. There was no difference in food utilization efficiency, suggesting that the changes seen were due to impalatability of the test article.

No treatment-related clinical pathology effects were seen. No treatment-related gross pathology or histopathological effects were noted. No differences in neoplastic incidences were noted.

Ophthalmoscopic examinations were performed by two ophthalmologists, neither of which judged the observed lesions to be treatment-related.

B. Reviewer's Discussion - Male and female rats (50/sex/group main study; 10/sex/group interim sacrifice) were fed diets containing amine oxide at levels of 0, 0.01, 0.1, or 0.2% [achieved doses of 0, 4.24/5.23, 42.3/52.6, or 87.4/107 mg/kg/day (M/F)] for 104 weeks. Dietary analyses confirmed that nominal diet concentrations were achieved.

No significant differences were observed in survival rates in either sex of the treated groups throughout the study when compared to the respective control groups. At termination (104 weeks), survival rates ranged from 48%-68% in males and 51%-68% in females. Clinical signs, hematological parameters, and urinalysis were also unaffected by treatment.

A significant, dose-dependent decrease in serum globulin occurred in males at 104 weeks (control - 4.1 g/dl; low-dose - 3.8 g/dl, p=not significant; mid-dose - 3.7 g/dl, $p<0.01$; high-dose - 3.6 g/dl, $p<0.01$), but the decreases were small (↓7-12% vs controls) and are not considered to be of toxicological concern. Serum globulin levels were unaffected in females. All other differences in clinical blood chemistry parameters between rats in the treated and control groups did not appear to be either treatment-related.

There were no differences of toxicological concern in absolute or relative organ weights at either the interim or terminal necropsy. Increases in relative organ weights were due to the decreased body weights.

Body weights were significantly lower ($p<0.05$-0.001) for males (↓9-14% vs controls) and females (↓5-14% vs controls) in the high-dose treatment group at 7 of 8 timepoints. The reductions at the remaining timepoint (week 39) were within the range of the other reductions (males - ↓11%; females - ↓8%), but were not statistically significant.

Mean food consumption (g/rat/day) was occasionally significantly decreased in high-dose males (↓5-10% vs controls; 5/8 periods; $p<0.01$ or 0.001) and high-dose females (↓4-7% vs controls; 6/8 periods; $p<0.05$-0.001). There were no significant differences in food utilization between the treated and control groups.

There was an increase in bilateral cataracts/opacities in the high-dose male rats (↑167% vs controls) at final necropsy. During study weeks 66 to 104, the incidence of bilateral cataract/opacities in the high-dose females was 2.4-6.4% vs 0% in the controls. The rats were examined by two different ophthalmologists, both of whom did not attribute any findings to the treatment. However, when compared to the sub-chronic toxicity study (MRID 44475203), in which 12/20 males and 8/20 females had lenticular cataracts/opacities in the 0.4% treatment groups at 13 weeks, it may be possible that a treatment-related effect is being observed.

No treatment-related microscopic postmortem differences were observed between rats in the treated and the control groups. All abnormalities appeared to occur randomly and sporadically in all study groups.

In conclusion, the dose levels employed in this study were adequate to characterize the chronic toxicological potential of amine oxide in both sexes of rats. Chronic toxicity was characterized in the high-dose males and females by reduced body weight and food consumption, and increased bilateral opacities/cataracts.

The chronic LOEL is 0.2% [87.4/107 (M/F) mg/kg/day] based on decreased body weight and ophthalmological opacities/cataracts. The chronic NOEL is 0.1% [42.3/52.6 (M/F) mg/kg/day].

Under the conditions of this study, amine oxide did not show any signs of oncogenicity it CD rats.

The submitted study is classified as **acceptable (§83-5(a))** and satisfies the guideline requirements for a chronic toxicity study (§83-1) and a carcinogenicity study (§83-2) in rats.

C. Study deficiencies -The ophthalmoscopic examination data were not submitted in summary form.