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

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JUL 26 1993

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Evaluation of Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) in the Combined Chronic Toxicity/Oncogenicity Study in Rats. Guideline Series 83-5. (MRID 419475-01)

Tox Chem No.: 016E
EPA ID No.: 069105
DP Barcode No.: D167336
Submission No.: S400617
Case No.: 819070

FROM: Brian Dementi, Ph.D., D.A.B.T. Brian Dementi 7/15/93
Review Section III
Toxicology Branch I
Health Effects Division (H7509C)

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Reregistration Branch
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THRU: Karen Hamernik, Ph.D.
Section Head, Review Section III
Toxicology Branch I
Health Effects Division (H7509C) K. Hamernik 7/16/93 KB 7/20/93

The Data Evaluation Review for the ADBAC combined chronic toxicity/oncogenicity study in rats, submitted by Chemical Specialties Manufacturers Association toward satisfying the Registration Guideline Series 83-5 testing requirement is herewith submitted to SRRD.

The test material was evaluated in the Sprague-Dawley rat via the dietary route of administration for two years at dosage levels of 0, 300, 1000 and 2000 ppm. There was no evidence of carcinogenicity under the conditions of the study. With respect to systemic toxicity, LOEL = 2000 ppm (decreased body weight, body weight gain and food consumption); NOEL = 1000 ppm. The study is rated Core Minimum. For further details please see the Data Evaluation Review with attached Addendum regarding dose selection issue.

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MEMORANDUM

OFFICE OF
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SUBJECT: Addendum to the Clement Data Evaluation Review for the combined chronic/oncogenicity study of ADBAC in the rat: dose selection issue. (MRID 419475-01)

FROM: Brian Dementi, Ph.D., D.A.B.T. Brian Dementi 5/4/93
Review Section III
Toxicology Branch I
Health Effects Division (H7509C)
Karl Baetcke 5/4/93

TO: ADBAC File
(RETAIN WITH DER)

In order to validate that 2000 ppm ADBAC was an MTD, the 90-day and 14-day range finding studies cited in the study were visited. The 90-day study, which evaluated doses of 0, 100, 500, 1000, 4000 and 8000 ppm, clearly revealed excessive mortality at 4000 and 8000 ppm. There was no clear dose related toxicity apparent at the lower doses. We should note the steep dose response for mortality. The 14-day study followed with doses of 0, 2000 and 3000 ppm. There was no mortality at any dose. Toxic signs at 3000 ppm included 100% incidence of loose feces, decreased food consumption and decreases in body weight. Also observed were excessive intestinal fluid and gas. At 2000 ppm slight changes in food consumption and body weight were observed. Gas filled ceca remained a problem of some degree.

The Registrant's representatives visited the Agency in February 1988 to discuss dose selection based upon findings in the above studies. The Registrant initially proposed doses of 0, 300, 1000 and 2500 ppm for the 2-year study. Agency representatives suggested a high dose of 1000-2000 ppm. The Registrant subsequently elected to go with doses of 0, 300, 1000 and 2000 ppm.

In view of findings in the various studies, including the 2-year study itself, and deliberations that preceeded dose selection, it would appear that doses for the definitive study of 0, 300, 1000 and 2000 ppm were properly chosen and that an MTD was achieved.

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[D167336]
Tox Chem No: 016E
PC Code : 069105

DLC 93066

FINAL

DATA EVALUATION REPORT

Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) 010428

Study Type: Combined Chronic Toxicity/Oncogenicity in Rats

Prepared for:

Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

August 17, 1992

Principal Author Carrie Rabe Date 8/17/92
Carrie Rabe, Ph.D.

Reviewer Date 8-12-92
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QA/QC Manager Sharon Segal Date 8/17/92
Sharon Segal, Ph.D.

Contract Number: 68D10075
Work Assignment Number: 1-51
Clement Number: 91-168
Project Officer: James E. Scott

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Guideline Series 83-5: Combined Chronic Toxicity/Oncogenicity in Rats

EPA Reviewer: Brian Dementi, Ph.D.
Review Section III, Toxicology Branch I
Health Effects Division

Signature:
Date: 6/20/92

EPA Acting Section Head:
Karen Hamernik, Ph.D., Review Section III
Toxicology Branch I, Health Effects Division

Signature:
Date: 6/8/93

DATA EVALUATION REPORT

STUDY TYPE: Combined chronic toxicity/oncogenicity in rats

TEST MATERIAL: Alkyl dimethyl benzyl ammonium chloride (ADBAC)

TOX. CHEM. NUMBER: 016E

P.C. NUMBER: 069105

SYNONYMS: Benzalkonium chloride

CAS Number: 68391-01-5

STUDY NUMBER: 53-543

MRID NUMBER: 419475-01

SPONSOR: ADBAC QUAT Joint Venture/
Chemical Specialties Manufacturers Association
1913 Eye Street, N.W.
Washington, D.C. 20006

TESTING FACILITY: Bushy Run Research Center
6702 Mellon Road
Export, PA 15632

TITLE OF REPORT: Chronic Dietary Toxicity/Oncogenicity Study with Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) in Rats

AUTHORS: M.W. Gill, S.J. Hermansky, and C.L. Wagner

REPORT ISSUED: Completion date, July 8, 1991

CONCLUSIONS: ADBAC was administered via the diet to Sprague-Dawley rats for 104 weeks at doses of 0, 300, 1,000, and 2,000 ppm. The average daily intake values of ADBAC at these dietary levels were 13, 44, and 88 mg/kg/day for males and 17, 57, and 116 mg/kg/day for females. ADBAC was not oncogenic under the conditions of this study. Systemic toxicity, as indicated by decreased body weight, body weight gain, and food consumption, occurred with a LOEL of 2,000 ppm and a NOEL of 1,000 ppm. The following treatment related effects were observed:

300 ppm -- Equivalent to 13 mg/kg/day in males and 17 mg/kg/day in females. No treatment-related effects were observed.

1,000 ppm -- Equivalent to 44 mg/kg/day in males and 57 mg/kg/day in females. No treatment-related toxicity was observed.

2,000 ppm -- Equivalent to 88 mg/kg/day in males and 116 mg/kg/day in females. Male and female body weights were decreased by approximately 5% and 6%, respectively. Male and female body weight gains were decreased by approximately 11% and 14%, respectively. Food consumption was significantly decreased in both males and females. In general, the effects on body weight and body weight gain paralleled the effects on food consumption. No treatment-related toxicity was observed based on clinical pathology parameters, and gross and microscopic pathology did not reveal any evidence of toxicity in the treated animals.

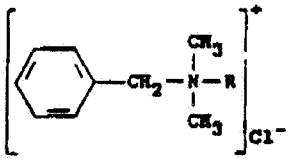
CORE CLASSIFICATION: This study is classified as Core Minimum for combined chronic toxicity/oncogenicity studies because although adequate toxicity as shown by at least a 10% decrease in body weight gain was demonstrated in both males and females, a palatability problem may have contributed to the effects observed on body weight and body weight gain.

A. MATERIALS, METHODS, AND RESULTS

1. Test Article Description

Name: Alkyl dimethyl benzyl ammonium chloride (ADBAC)

Formula: A mixture of alkyl dimethyl benzyl ammonium chlorides of the general formula in which R represents a mixture of the alkyls from $C_{12}H_{25}$ to $C_{16}H_{33}$. The distribution analogs with alkyl chain lengths of 12, 14, and 16 were 40%, 50%, and 10%, respectively.



Lot number: 7293K

Purity: 81.09% active ingredient; the sponsor indicated that the substance also contained ethanol (10-15%)

Physical property: Pale-yellow, viscous liquid

Stability: Stable for at least 14 days when stored at room temperature

2. Rationale for Dose Selection

Dietary levels of ADBAC for the current study were selected based upon the results of 14-day and 90-day dietary range-finding studies (BRRC report numbers 51-513 and 51-503, respectively). The doses selected for the current study were intended to produce toxicity at the high dose and no toxicity at the low dose. The specific toxic end points used to set the doses for the current study were not

stated. However, loose feces were reported in the range-finding studies at higher doses than those used in the current study (actual doses associated with loose feces in the range-finding studies were not presented in the current study).

The dietary levels selected for the current study were 0, 0, 300, 1,000, and 2,000 (two control groups were used).

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3. Test Article Analyses for Purity and Stability

ADBAC is a mixture of alkyl dimethyl benzyl ammonium chlorides. The purity of the test material was not verified by the testing facility. However, samples of the test material were sent to the sponsor a week after the start of the study and then at 5-7-month intervals to determine purity. The percent active ingredient reported by the sponsor ranged from 79.6% to 81.5%. Test diets were prepared using a correction for purity of 81.09%.

Test diets were prepared by mixing appropriate amounts of ADBAC (correcting for purity) with rat chow to obtain a concentrated premix. Actual dietary concentrations were obtained by serial dilutions of the premix with rat chow. The weight of the premix used to prepare the test diets was found to decrease during mixing because of evaporation of ethanol (found in the test material). Corrections were made for the ethanol evaporation when making the dilutions of the premix. Fresh test diets were prepared weekly and stored at room temperature in a closed container until offered to the rats.

Stability of the test material in the diet at room temperature in open feed jars was measured after up to 14 days and in closed storage containers after up to 21 days. No loss of test material was observed.

Homogeneity of sample batches of the test material batches was tested prior to the initiation of the study and was found to be acceptable. The actual concentration of the test material in diets offered to the rats was measured every week for the first 4 weeks of the study and then every 4 weeks, thereafter. The average measured concentrations at each test level were as follows:

Nominal Concentration (ppm)	Measured Concentration[a] (ppm)
300	307.5 ± 12.6
1,000	1,035.4 ± 45.1
2,000	2,049.3 ± 99.6

[a]Mean ± S.D. calculated by the reviewer, data from Table 4, Appendix 1

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4. Animals

Rats (380 males and 380 females, Sprague-Dawley CD®) were received from Charles River Laboratories, Inc., Portage, MI. The rats were approximately 32 days old upon arrival and were caged 2 rats/cage for approximately 1 week. Thereafter, rats were individually caged in stainless steel cages with wire mesh floors. The animal room was operated on a 12-hour light/dark cycle, and temperature and relative humidity were maintained at 66°-77°F and 40%-70%, respectively, with at least 8 room air changes per hour. Water and food (Purina® Certified Rodent Chow #5002 ground meal) were provided ad libitum. Within 2 days of arrival, 10 rats of each sex (randomly selected) were selected for tests for fecal parasites and viruses (5/sex), clinical laboratory studies (10/sex), and gross (10/sex) and histopathologic (3/sex) examination to verify that the shipment of rats was free of infectious diseases and parasites. Rats were randomized by body weight and allocated to study groups (60/sex/dose) using a computerized procedure such that all groups of the same sex had similar mean body weights. The rats were approximately 8 weeks old, and males and females ranged in weight from 247 to 309 g and from 162 to 215 g, respectively, at the time of the first exposure to test diets. Rats were uniquely identified through use of cage tags, ear notching, and toe clipping techniques.

5. Statistical Analyses

Data with homogeneous variances (as determined using Levene's test) were analyzed using analysis of variance. If the result was significant ($p \leq 0.05$), pooled variance t-tests were used to analyze for differences between the control and other study groups. Data with heterogeneous variances were analyzed using analysis of variance for unequal variances, followed by variance t-tests. Nonparametric data were analyzed using the Kruskal-Wallis test or the Mann-Whitney U test. Fisher's exact test was used to analyze incidence data. The limit for statistical significance was set at 0.05 for all tests.

6. General Observations

(a) Mortality/moribundity/survival

Animals were observed twice daily (once in the morning and once in the afternoon) for mortality/moribundity.

Mortality of the male and female treatment groups ranged from 38% to 47% and from 38% to 50%, respectively. No treatment-related effects on the incidence of mortality or on mean survival time were observed.

(b) Clinical observations

Animals were observed daily for overt adverse clinical signs. In addition, detailed clinical observations (including palpations) were made once per week.

Loose feces were observed more frequently in treated males at all doses than in controls. Although the number of affected animals did not clearly increase with dose, the onset was somewhat earlier in males given diets containing 1,000 and 2,000 ppm ADBAC. This effect was not considered to be biologically significant because review of the individual animal data by the reviewers did not clearly indicate any dose-related trends in the number of the animals affected or in the frequency with which it was observed among affected animals.

The incidence of palpable masses in male and female rats was not increased above controls at any dose level.

(c) Body weights/food consumption/feed efficiency/test article intake

Body weights--Individual body weights were determined weekly for the first 14 weeks of the study and then every 2 weeks, thereafter.

Body weight data from selected intervals are presented in Table 1. Body weights of the high-dose males were consistently significantly decreased relative to both control groups during weeks 1-26 and then sporadically thereafter. Similarly, body weights of the high-dose females were consistently significantly decreased relative to both control groups during weeks 1-60. The body weights of males and females in the high-dose group remained less than the controls, but not statistically significantly, for the remainder of the study. The decrease in male body weights ranged from 3% to 7% (average, 5%) below control values and the decrease in female body weights ranged from 2% to 9% (average, 6%) below control values.

Body weight gain data from selected intervals are presented in Table 2. Body weight gains for both males and females at the high dose were significantly decreased for weeks 1-36 and 1-60, respectively, and remained lower (but not statistically significantly) than controls throughout the study. Male body weight gains ranged from 7% to 26% (average, 11%) below control values. Female body weight gains ranged from 9% to 36% (average, 14%) below control values.

Food consumption--Individual food consumption values were determined weekly.

Food consumption data from selected intervals are presented in Table 3. Food consumption was repeatedly decreased in males at both 1,000 and 2,000 ppm and in females at 2,000 ppm. Food consumption in males was significantly decreased relative to both control groups during weeks 2, 3, 5, 8, 11, 12, 32, 34, 54, and 60 at 1,000 ppm and during weeks 1, 3-8, 11-14, [illegible], 28, 30, 32, 44, 46, 48, 54, 56, 60, 64, 70, and 88 at 2,000 ppm. Food consumption in females was significantly decreased relative to both control groups only during week 5 at 1,000 ppm and during weeks 1, 2, 5-10, 12, 22, 34, 48, 50, 54, and 78 at 2,000 ppm.

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In the absence of significant effects on male body weight at 1,000 ppm, the decreased food consumption at 1,000 ppm is not considered to be a biologically significant effect.

Feed efficiency--Feed efficiency was not determined in this study.

Test article intake--Test article intake (mg ADBAC/kg/day) was calculated weekly for the first 14 weeks of the study and every other week, thereafter. The report does not state whether the values were calculated using the nominal or actual dietary concentrations of ADBAC.

The study authors calculated that intake values of ADBAC for male rats receiving diets containing 300, 1,000, and 2,000 ppm were 13, 44, and 88 mg/kg/day, respectively. The intake values for female rats receiving these same dietary concentrations were 17, 57, and 116 mg/kg/day, respectively.

(d) Ophthalmoscopic examination

Eye examinations were conducted by indirect ophthalmoscopy and biomicroscopy prior to the first exposure and at the end of the test period on all surviving rats.

No treatment-related effects on the appearance of the eyes were observed.

7. Clinical Pathology

Hematology and clinical chemistry analyses were performed on 15 rats/sex/dose at 26, 52, 78, and 104 weeks. Blood samples were obtained from the retroorbital sinus of rats that had been fasted overnight. Urinalysis was performed at 25, 51, 77, and 103 weeks. Urine samples were obtained from metabolism cages in which animals had been housed for 24 hours. Animals in the metabolism cages had access to test diets and water. The same animals used for hematology and clinical chemistry determinations were used for urinalysis (whenever possible).

(a) Hematology

The parameters marked with an "X" were examined.

X Hematocrit (HCT)*
X Hemoglobin (HGB)*
X Leukocyte count (WBC)*
X Erythrocyte count (RBC)*
X Platelet count*
X Reticulocyte count (RETIC)
X Leukocyte differential count*
X Mean corpuscular HGB (MCH)
X Mean corpuscular HGB concentration (MCHC)
X Mean corpuscular volume (MCV)

* Recommended by Subdivision F (November 1984) Guidelines

No biologically significant treatment-related effects on hematology were observed. A statistically significant decrease in the number of segmented neutrophils at week 26 and a significant decrease in hematocrit at week 52 were observed in high-dose females. However, the changes were not persistent and were small and not considered to be biologically significant.

(b) Blood (clinical) chemistry

Blood chemistry analyses included the parameters marked below with an "X".

Electrolytes	Other
X Calcium*	X Albumin*
X Chloride*	X Albumin/globulin ratio
X Sodium*	X Blood creatinine*
X Phosphorus*	X Blood urea nitrogen*
X Potassium*	X Total cholesterol*
	X Globulin
Enzymes	X Glucose*
	X Total bilirubin*
X Creatine phosphokinase*	X Direct bilirubin
X Alkaline phosphatase (ALP)	X Indirect bilirubin
X Gamma glutamyltransferase (GGT)	X Total protein*
X Serum alanine aminotransferase (SGPT)*	
X Serum aspartate aminotransferase (SGOT)*	

* Recommended by Subdivision F (November 1984) Guidelines

No biologically significant treatment-related effects on blood chemistry values were observed. A statistically significant increase in urea nitrogen and chloride were observed in high-dose males at week 52. However, these changes were observed only at that interval and were too small to be considered biologically significant.

(c) Urinalysis

Urinalysis included the parameters marked below with an "X".

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

* Recommended by Subdivision F (November 1984) Guidelines

Urinary volume, specific gravity, and pH were analyzed statistically. Other urinary parameters were presented as frequency data. The only statistically significant change that appeared to be treatment related was a significant decrease in urinary volume at week 103 in males receiving diets containing

2,000 ppm ~~(Table 5)~~. However, in the absence of other indicators of increased renal toxicity in high-dose males (changes in other urinary or blood parameters or an increase in the incidence of microscopic evidence of renal toxicity), the biological significance of this finding is questionable.

8. Sacrifice and Pathology

All rats that died, were sacrificed in extremis, or were sacrificed as scheduled, received a complete gross examination. Tissues from both control groups and the group that received the highest dietary level that are marked with an "X" below were examined histologically. In addition, microscopic examination of lungs, liver, kidneys, and all gross lesions of low- and mid-dose groups was also performed. All tissues were preserved in neutral buffered 10% formalin solution and organs that are marked with a "XX" were also weighed at necropsy.

Digestive System	Cardiovascular/Hematologic	Neurologic
X Pancreas*	X Aorta*	XX Brain*
X Salivary glands*	XX Heart*	X Peripheral nerve* (sciatic nerve)
X Esophagus*	X Bone marrow*	X Spinal cord* (three levels)
X Stomach*	X Lymph nodes*	X Pituitary*
X Duodenum*	XX Spleen*	X Eyes*
X Jejunum*	X Thymus*	
X Ileum*		
X Cecum*	Urogenital	
X Colon*		
X Rectum*	XX Kidneys*	Glandular
XX Liver*	X Urinary bladder*	
	XX Testes*	XX Adrenals*
Respiratory	X Epididymides*	X Lacrimal gland
	X Prostate*	X Mammary gland*
X Trachea*	X Vagina*	X Thyroids*
X Lungs* (with mainstem bronchi)	XX Ovaries*	X Parathyroids*
	X Uterus*	
	X Seminal vesicles*	

Other

X Bone (sternum and femur)*
X Skeletal muscle (thigh)*
X Skin*
X All gross lesions and masses*

* Recommended by Subdivision F (November 1984) Guidelines

(a) Macroscopic

Very few gross lesions were observed in either the control or treated animals. No treatment-related lesions were apparent.

(b) Organ weights, organ-to-body weight, and organ-to-brain weight ratios

No treatment related changes were observed in the organ weights or organ-to-body or organ-to-brain weight ratios. The only statistically significant differences between organ weights of treated rats and those of the corresponding controls was a significant decrease (11%) in the absolute heart weight and a significant decrease (9%) in heart-to-brain weight ratio of high-dose female rats. This was considered to be an incidental finding because the heart-to-body weight ratio was not similarly decreased in high-dose females relative to controls.

(c) Microscopic Examination

Nonneoplastic--No nonneoplastic microscopic lesions were significantly elevated in the high-dose group when compared to both control groups. Most microscopic lesions that were observed were those commonly associated with aging rats and were comparable in incidence among both control and treated rats. The most common nonneoplastic microscopic lesions observed in male rats were those associated with chronic renal disease. In females, chronic renal disease was also observed, but much less frequently and to a lesser degree than in males. A number of lesions associated with pituitary tumors (see neoplastic lesions, below) were also observed (adrenal cortical cell hypertrophy, hypersecretion of mammary gland, compression of the brain).

Full histopathology of tissues of the high-dose group and both control groups was performed. However, full histopathology on all animals that died or were killed during the study was apparently not performed (this is recommended by the Subdivision F [November 1984] Guidelines). Histopathology of the mid- and low-dose groups was limited to the lungs, liver, kidneys, and all gross lesions. Microscopic findings in the mid- and low-dose groups were not compared statistically with the control group data. It is doubtful that the absence of full histopathology on the animals in the mid- and low-dose groups that died during the study could have affected the interpretation of the results as no increases in any lesions were observed in the high-dose rats.

Neoplastic--The most frequently observed neoplasms included pituitary tumors in both sexes and mammary gland tumors in females. However, they occurred with similar frequencies in both the high-dose and control groups and, along with other sporadically observed neoplasms, were not considered to be treatment related.

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A signed Good Laboratory Practice Compliance Statement, a signed Quality Assurance Statement, and a list of Quality Assurance Inspections were included.

B. DISCUSSION

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The design and conduct of this study were complete and adequate, and the summary table data were supported by the individual animal data. The data were well reported, and the statistics used were appropriate.

The dietary levels selected for this study (0, 300, 1,000, and 2,000 ppm) were based on the results of range-finding studies and were intended to produce toxic effects at the highest dose tested. However, the details and results of the range-finding studies were not presented; therefore, it is difficult to know what toxic end point was used in setting doses. The toxicity observed in the current study was limited to effects on body weight, body weight gain, and food consumption. At the highest dose tested, male and female body weights were depressed by approximately 5% and 6%, respectively; male and female body weight gains were depressed by approximately 11% and 14%, respectively; and male and female food consumption were depressed by approximately 6% and 4%, respectively (% change values were averaged over the entire length of the study). The decreases in body weight, body weight gain, and food consumption were observed primarily during the first year of the study, and the time courses of these effects were essentially parallel. Although palatability problems may have contributed to the decreased food consumption and effects on body weight, the possibility of test material toxicity cannot be eliminated. The NOEL/LOEL for systemic toxicity based on the body weight and food consumption effects were 1,000 ppm (NOEL) and 2,000 ppm (LOEL). No evidence of oncogenicity of the test material was observed.

TABLE 1. Mean Body Weight at Representative Intervals in Rats Given Diets Containing ADBAC[a,b]

Dietary Level (ppm)	Mean Body Weight (g ± S.D.) at Week: 0	1	7	13	26	52	78	104
				Males				
0	282±13	322±18	450±32	506±47	589±54	667±80	698±90	685±106
300	282±14 (+0.3%)	321±20 (+0.3%)	458±42 (+1.3%)	519±53 (+2.5%)	602±69 (+2.0%)	680±87 (+1.2%)	707±99 (+0.1%)	626±105 [c] (-7.9%)
1000	280±15 (-0.2%)	319±20 (-0.3%)	444±41 (-1.7%)	500±47 (-1.4%)	582±68 (-1.5%)	661±86 (-1.7%)	696±99 (-1.5%)	691±88 (+1.8%)
2000	282±13 (+0.4%)	311±20 [d,e] (-2.7%)	429±38 [d,f] (-5.1%)	482±47 [d,f] (-5.0%)	564±61 [c,e] (-4.5%)	641±79 (-4.6%)	674±86 (-4.6%)	648±104 (-4.6%)
0	280±15	318±19	453±38	507±50	592±69	677±87	714±105	674±95
				Females				
0	186±11	204±13	257±19	280±22	312±29	379±44	423±64	444±83
300	188±10 (+0.4%)	203±12 (+0.3%)	257±19 (+0.3%)	278±23 (-0.3%)	308±34 (-0.6%)	368±60 (-1.7%)	423±84 (+0.8%)	420±98 (-4.4%)
1000	186±11 (-0.7%)	202±14 (-0.6%)	255±20 (-0.3%)	278±24 (-0.3%)	309±35 (-0.5%)	378±60 (+1.1%)	422±72 (+0.6%)	431±81 (-2.0%)
2000	187±10 (-0.3%)	197±12 [d,e] (-3.0%)	241±19 [d,f] (-5.7%)	263±18 [d,f] (-5.7%)	290±25 [d,f] (-6.3%)	346±44 [d,f] (-7.4%)	393±66 (-6.4%)	398±64 (-9.4%)
0	186±10	201±12	254±17	278±20	308±29	369±41	415±66	435±72

[a]Data extracted from Study #53-543, Tables 5 and 7.
[b]Number in parantheses is the percent change from the average control value, as calculated by the reviewers.
[c]Significantly different from the first control group; $p<0.05$.
[d]Significantly different from the first control group; $p<0.01$.
[e]Significantly different from the second control group; $p<0.05$.
[f]Significantly different from the second control group; $p<0.01$.

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TABLE 2. Mean Cumulative Body Weight Gains at Representative Intervals in Rats Given Diets Containing ADBAC[a,b]

Dietary Level (ppm)	Mean Cumulative Body Weight Gain (g ± S.D.) at Week: 0-1	0-7	0-13	0-26	0-52	0-78	0-104
				Males			
0	40±8	169±25	225±41	308±48	385±75	417±85	402±105
300	40±8 (+0.5%)	176±33 (+2.9%)	238±43 (+5.3%)	321±60 (+3.6%)	399±78 (+2.0%)	426±93 (+0.3%)	347±108 [c] (-12.8%)
1000	39±8 (-1.5%)	164±31 (-4.1%)	219±37 (-2.9%)	302±59 (-2.5%)	381±78 (-2.7%)	416±95 (-2.3%)	414±81 (+4.1%)
2000	29±10 [d,f] (-25.7%)	147±30 [d,f] (-14.2%)	200±38 [d,f] (-11.7%)	282±54 [c,f] (-9.0%)	359±79 [f] (-8.3%)	391±83 (-8.0%)	366±103 (-8.1%)
0	38±8	173±30	227±43	312±62	397±81	434±100	394±91
				Females			
0	16±7	69±13	92±17	124±25	190±42	235±61	255±81
300	16±5 (-0.6%)	69±14 (0%)	90±18 (-1.8%)	120±31 (-2.1%)	180±57 (-3.7%)	235±82 (+1.2%)	233±98 (-7.5%)
1000	16±6 (+1.3%)	69±13 (+0.7%)	93±18 (+0.7%)	123±29 (+0.1%)	192±54 (+2.9%)	237±67 (+2.2%)	245±79 (-2.6%)
2000	10±5 (-35.7%)	55±15 [d,f] (-20.3%)	77±12 [d,f] (-16.8%)	104±20 [d,f] (-15.4%)	160±46 [d,f] (-14.4%)	207±63 (-10.8%)	214±64 (-15.1%)
0	16±4	69±11	92±15	122±26	183±40	229±65	249±72

[a]Data extracted from Study #53-543, Tables 6 and 8.
[b]Number in parantheses is the percent change from the average control value, as calculated by the reviewers.
[c]Significantly different from the first control group; $p<0.05$.
[d]Significantly different from the first control group; $p<0.01$.
[e]Significantly different from the second control group; $p<0.05$.
[f]Significantly different from the second control group; $p<0.01$.

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TABLE 3. Mean Food Consumption at Representative Intervals in Rats Given Diets Containing ADBAC[a,b]

Dietary Level (ppm)	Mean Food Consumption (g ± S.D.) at Week: 0-1	6-7	12-13	25-26	51-52	77-78	103-104
				Males			
0	25.9±1.9	26.4±2.0	26.1±3.0	23.4±2.1	26.0±3.1	25.0±3.4	24.3±4.8
300	26.2±2.5 (-0.4%)	26.6±2.6 [e] (-1.5%)	26.7±2.3 (+2.9%)	24.1±2.9 (+3.4%)	25.5±2.8 (-2.9%)	24.6±5.0 (-2.8%)	21.9±6.0 (-8.6%)
1000	25.2±2.2 [f] (-4.1%)	25.8±2.4 [f] (-4.4%)	25.5±2.5 (-1.7%)	22.8±2.5 (-2.1%)	25.4±3.7 (-3.2%)	24.8±3.9 (-2.0%)	23.5±3.2 (-1.9%)
2000	22.7±3.1 [d,f] (-13.7%)	25.1±2.2 [d,f] (-7.0%)	24.1±3.8 [d,f] (-7.1%)	22.3±2.6 [c] (-4.3%)	25.6±2.9 (-2.5%)	24.2±4.1 (-4.3%)	24.4±4.1 (-1.9%)
0	26.7±2.0	27.6±2.3	25.8±3.0	23.2±2.9	26.5±3.5	25.6±4.7	23.6±6.4
				Females			
0	18.8±2.0	19.2±2.0	17.6±1.6	16.9±3.2	21.1±2.9	20.5±3.2	19.1±5.0
300	19.3±2.3 (+1.0%)	19.0±1.8 (+0.5%)	17.4±1.6 (-2.0%)	16.6±2.2 (+2.2%)	19.9±3.0 [c] (-1.7%)	20.4±4.1 (+0.7%)	19.9±5.4 (+4.7%)
1000	18.3±1.6 [f] (-4.2%)	18.9±1.9 (0%)	17.5±1.6 (-1.4%)	16.5±3.0 (+1.5%)	19.8±2.4 [c] (-2.2%)	19.3±2.8 (-4.7%)	18.0±4.8 (-5.3%)
2000	16.8±2.5 [d,f] (-12.0%)	17.6±2.0 [d,f] (-6.9%)	17.4±1.6 [d,f] (-2.0%)	15.8±3.2 [c] (-2.8%)	18.9±2.4 [d] (-6.7%)	18.4±3.4 [d,e] (-9.1%)	17.9±5.0 (-5.8%)
0	19.4±2.0	18.6±1.9	17.9±1.6	15.6±1.7 [c]	19.4±3.1 [d]	20.0±4.0	18.9±4.7

[a]Data extracted from Study #53-543, Tables 9 and 10.
[b]Number in parantheses is the percent change from the average control value, as calculated by the reviewers.
[c]Significantly different from the first control group; $p<0.05$.
[d]Significantly different from the first control group; $p<0.01$.
[e]Significantly different from the second control group; $p<0.05$.
[f]Significantly different from the second control group; $p<0.01$.

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