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

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AUG 11 1993

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: ADBAC: Review of 2-Generation Reproduction Study (MRID 413850-01)

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S400615
1-1953
Tox Chem No. 016E
PC Code 069105

FROM: Karen L. Hamernik, Ph.D.
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8/13/93

TO: Brigid Lowery, PM Team 72
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THRU: Karl Baetcke, Ph.D.
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Attached is the review of a two generation reproduction study in the Sprague-Dawley rat performed with Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) administered in the diet. The conclusions from the Data Evaluation Report are as follows:

Sprague-Dawley rats were administered 0, 300, 1000, or 2000 ppm of ADBAC daily in the diet over two generations. Clear evidence of toxicity was not observed even at the highest dose, although there were transient decreases in body weight gains and food consumption in F0 females at 2000 ppm. Consequently, the NOEL for parental toxicity was 2000 ppm (146 mg/kg/day male and female combined; 130.1 mg/kg/day, males and 160.9 mg/kg/day, females, averaged for the F0 and F1 generations). The LOEL for parental toxicity was not clearly established.

Reproductive toxicity seen at 2000 ppm (the LOEL) was evident as reduced pup body weights and body weight gain during lactation indicating an adverse effect on pup growth. Based on these results, the NOEL for developmental toxicity was 1000 ppm (73 mg/kg/day male and female combined; 65.4 mg/kg/day, males and 79.9 mg/kg/day, females, averaged for the F0 and F1 generations).

The study is considered to be Core Guideline for guideline 83-4.

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DOC930055

FINAL

DATA EVALUATION REPORT

ADBAC

Study Type: Reproductive Toxicity

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
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Contract Number: 68D10075
Work Assignment Number: 1-51
Clement Number: 91-166
Project Officer: James Scott

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Guideline 83-4: Reproductive Toxicity

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EPA Reviewer: Brian Dementi, Ph.D.
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Signature Brian Dementi, Ph.D.
Date 8/5/92

Acting EPA
Section Head: Karen Hamernik, Ph.D.
Review Section III, Toxicology Branch I/HED

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Date 8/3/93

DATA EVALUATION REPORT

STUDY TYPE: Reproductive toxicity

EPA IDENTIFICATION NUMBERS

Tox Chem. Number: 016E PC 069105

MRID Number: 413850-01

TEST MATERIAL: Alkyl dimethyl benzyl ammonium chloride

SYNONYMS: ADBAC; benzalkonium chloride

SPONSOR: ADBAC QUAT Joint Venture, Chemical Specialities Manufacturers Association, 1001 Connecticut Avenue, N.W., Washington, D.C.

STUDY NUMBER: 52-524

TESTING FACILITY: Bushy Run Research Center, R.D., #4 Mellon Road, Export, PA

TITLE OF REPORT: Two-Generation Reproduction Study in Sprague-Dawley (CD®) Rats With Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) Administered in the Diet

AUTHOR: T.L. Neeper-Bradley

STUDY COMPLETION DATE: January 30, 1990

REPORT ISSUED: January 30, 1990

CONCLUSIONS: Sprague-Dawley rats were administered 0, 300, 1000, or 2000 ppm of ADBAC daily in the diet over two generations. Clear evidence of toxicity was not observed even at the highest dose, although there were transient decreases in body weight gains and food consumption in F_0 females at 2000 ppm. Consequently, the NOEL for parental toxicity was 2000 ppm (146 mg/kg/day); the LOEL for parental toxicity was not clearly established. Should be: Female Combined

Reproductive toxicity seen at 2000 ppm was evident as reduced pup body weights and body weight gain during lactation indicating an adverse effect on pup growth. Based on these results, the NOEL for developmental toxicity was 1000 ppm (65.4 mg/kg/day, MALES; 79.9 mg/kg/day, FEMALES), AND THE LOEL WAS 2000 ppm (130.1 mg/kg/day, MALES; 160.9 mg/kg/day, FEMALES). BAD 4/15/93

[redacted]

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CORE CLASSIFICATION: Core ~~Minimum~~ Data. This study meets the ~~minimum~~ requirements set by Guideline 83-4 for a two-generation reproductive study in rats, ~~because no LOEL for parental toxicity was established.~~

A. MATERIALS

Test Compound

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Alkyl composition: C-12, 40%; C-14, 50%; C-16, 10%
Purity: 81.09% manufacturing use product (supplier analysis); contaminants not reported
Stability: Not reported
Specific gravity: Not reported
Description: Pale-yellow viscous liquid
Lot number: 7293K
Batch number: BRRC 50-512 A through E
Receipt date: November 11, 1987
Other provided information: Stored in freezer

Vehicle(s): None. The test material was administered orally through the diet.

Test Animal

Species: Rat
Strain: Crl:CD®(SD)BR
Source: Charles River Breeding Laboratories, Kingston, NY
Age: 27 days old upon arrival
Body weight: At initiation of study, males weighed approximately 75 g, and females weighed approximately 65 g.

B. STUDY DESIGN

The study was designed to evaluate the potential reproductive and developmental effects in rats produced by dietary administration of ADBAC for two generations. Upon arrival, rats were quarantined for approximately 2 weeks prior to initiation of treatment so that representative animals could be examined by a veterinarian to determine general animal health.

Animal Husbandry: Animals were identified by a stainless steel ear tag. Animals were housed two/sex/cage during the quarantine period, and singly thereafter. Food (Ralston-Purina® Certified Ground Rodent Chow No. 5002) and tap water were provided ad libitum. Environmental parameters were as follows: light -- 12-hour light/dark cycle; temperature -- 66-73°F; relative humidity -- 40-60%. Although the temperature and relative humidity in the animal quarters were outside the desired ranges on some occasions, no adverse effect on animal health was apparent.

Mating Procedure: After 10 weeks of dietary treatment, the F_0 parental animals were mated. The F_1 parental animals were mated after 15 weeks of dietary treatment.

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Each female was housed with one randomly selected male from the same dose group. Each breeding regimen consisted of a 7-21-day cohabitation period. Females were observed once daily for the presence of sperm and twice daily for the presence of copulation plugs. The day that a copulation plug or vaginal sperm was observed was designated gestation day (GD) 0. Sibling matings were avoided.

Group Arrangement: F_0 and F_1 animals were randomly assigned to the following dose groups using a computer-generated stratified weight randomization program:

Test Group	Dose Level (ppm)	Number Assigned per Group			
		F_0		F_1	
		Males	Females	Males	Females
Control	0	28	28	28	28
Low dose	300	28	28	28	28
Mid dose	1000	28	28	28	28
High dose	2000	28	28	28	28

Dose Administration: ADBAC was administered in the diet continuously for two successive generations. Dietary preparations of the test material were corrected for the percent active ingredient. The rationale for selection of dose levels was not provided in the study report. Diets were prepared weekly from a premix consisting of the test substance and ground chow combined in a Hobart mixer. The premix was diluted with control diet to obtain the desired dose levels. Test diets were stored at room temperature in polyethylene containers. Animals received the test substance in the diet for 10 and 15 weeks prior to breeding of the F_0 and F_1 generations, respectively.

Homogeneity and stability analyses were performed prior to the initiation of treatment. Homogeneity of the test substance in the diet was determined from a total of nine samples (three from each of three layers-top, middle, and bottom) of the diet. Stability analyses were conducted on the high- and low-dose diets at room temperature in open glass containers and closed polyethylene containers. Test substance concentration in the diets was determined using high-pressure liquid chromatography weekly for the first 4 weeks of the study, and monthly, thereafter.

Observations: During the premating period, animals were observed twice daily for signs of toxicity and/or mortality. Clinical examinations were conducted once daily for the remainder of the study. Prior to breeding, body weights and food consumption for all animals were also determined weekly. Mated females were weighed on days 0, 6, 15, and 20 of gestation. Dams that delivered litters were weighed on postnatal days 0, 7, 14, and 21. A similar protocol was used for the F_1 generation.

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The following data were recorded for each litter: 010484

- the numbers of pups born (live, dead, and total);
- survival indices at 0, 4, 7, and 14 days after birth and at weaning;
- litter weights on days 1, 4, 7, and 14 after birth, at weaning, and at postnatal day 28;
- clinical observations of pups during the pre-weaning period (birth to day 21 postpartum);
- individual weights on day 21 postparturition; and
- necropsy findings in stillborn pups and pups that died during lactation.

On day 4 postpartum, pups were culled and litter size was adjusted to four males and four females using a computer-randomization method. Pups were randomly selected to serve as the F_1 parental animals.

F_0 and F_1 adults in all groups were necropsied. Animals were anesthetized with methoxyflurane and were euthanized by severing the brachial blood vessels. The following tissues were collected from all parental animals, fixed in a 10% buffered formalin solution, embedded in paraffin, and sectioned and stained with hematoxylin and eosin:

- Ovaries
- Uterus
- Vagina
- Other tissues with gross lesions
- Testes
- Epididymides
- Seminal vesicles
- Prostate

Histologic examination was performed on the above tissues of all F_0 and F_1 adult rats from the high-dose and control groups, and on any of the above tissues displaying gross lesions from the low- and mid-dose animals. All parental animals that died during treatment were necropsied, and complete histopathological examinations were performed.

The uteri of nonpregnant F_0 and F_1 females were immersed in a 10% buffered formalin solution for verification of implantation.

A gross internal examination was performed on any pup that appeared abnormal or moribund during the study. In addition, 10 randomly selected pups per sex per test group were selected from the F_1 and F_2 generations for gross internal examination.

Statistical Analysis: The following analyses were conducted:

- Body weights, food consumption, and organ weights were analyzed using Levene's test for equal variances, analysis of variance (ANOVA), and t-tests with a Bonferroni correction.

- Nonparametric analyses were conducted using the Kruskal-Wallis test followed by the Mann-Whitney U-test for pairwise comparisons.

- Fischer's exact test was used to compare frequency data.

For all statistical tests, a 0.05 (two-tailed) level of significance was used.

Compliance

- A signed Statement of Compliance with Good Laboratory Practice Standards, dated January 22, 1990, was submitted.
- A signed Quality Assurrance Statement, dated January 30, 1990, was provided.
- A signed but undated Statement of No Data Confidentiality Claim was submitted.

C. RESULTS

1. Test Material Analysis

Analysis of the test diets revealed that the concentrations ranged from 95.3% to 109.0% of the nominal level for low-dose diets, from 95.6% to 107.9% of the nominal level for mid-dose diets, and from 94.7% to 108.0% of the nominal level for high-dose diets. Stability of the test material in the 300- and 2000- ppm diets (stored at room temperature for 21 days in a closed polyurethane container) was between 104.3% and 104.7% of the nominal level for the low-dose diet, and between 103.4% and 105.2% of the nominal level for the high-dose diet. For preparations held in an open glass container for 14 days, stability ranged from 101.3% to 101.6% of the nominal level for low-dose diets and from 103.5% to 106.4% of the nominal level for high-dose diets. Homogeneity analyses revealed concentration ranges of 103.7-114.3%, 98.5-111.6%, and 103.8-111.8% of the nominal level for the low-, mid-, and high-dose diets, respectively.

2. Parental Toxicity

Mortality: No treatment-related mortality was observed. One high-dose F_1 male was sacrificed in a moribund condition on study day 50 because of a cage accident. Necropsy findings revealed abnormal contents in the gastrointestinal tract, pharyngeal malocclusion, and reduced spleen size.

Clinical Observations: No treatment-related clinical signs of toxicity were observed in the F_0 generation. Incidental clinical findings were observed in all groups of both sexes and generations and included periocular encrustation, swelling of the nose, dental problems, and alopecia.

Body Weight: Summaries of body weight gain from selected time intervals are presented in Tables 1, 2, and 3. Although decreases in body weights and/or body weight gains were noted in F_0 and F_1 parental animals at 2000 ppm during the premating period, because of the large standard deviations in the reported values these effects were not considered biologically significant by the reviewers. Detailed results are presented in the text.

In the F_0 generation, body weights (data not shown) at 2000 ppm were slightly lower (4%) than controls for males throughout the premating and postmating periods. Sporadic significant ($p<0.01$) increases or decreases in body weight gain at 2000 ppm and significant ($p\leq0.01$) increases (≥5%) at 1000 ppm were not considered to be treatment related. For females at 2000 ppm, there was a significant ($p<0.05$) reduction (4%-5%) in body weight during weeks 5, 6, 9, and 10 of the premating period (data not shown). Body weight gain of these females was significantly ($p<0.01$) reduced (62%) during weeks 8-9; this effect was not considered biologically significant by the reviewers because of the high standard deviations. Similarly, the 84% weight reduction compared to controls at weeks 9-10 for high-dose females was neither biologically nor statistically significant because of the low weight gain in the control group at this interval. During gestation at 2000 ppm, the body weight (data not shown) but not the body weight gain (Table 2) was significantly ($p<0.05$) lower (=5%) for treated females than for controls only on day 0 of gestation. These dams gained an average of 3.27 g on days 14-21 of lactation compared to an average weight loss of 9.12 g in the control group (Table 3).

In the F_1 generation, male body weights were lower (5%) at 2000 ppm or higher (5%) at 1000 ppm (during week 5; data not shown) than controls for the premating period. There was a significant ($p\leq0.01$) increase in body weight gain at 1000 ppm (18% increase, weeks 2-3; 216% increase, weeks 13-14) and a decrease (11%) at 2000 ppm (weeks 1-2) compared to controls. Because of the sporadic occurrence of effects and large standard deviations in the reported values, these findings were considered to be incidental. For females, significant increases in body weights ($p<0.01$) at 1000 ppm (data not shown) and body weight gains (≥40%) at 300 and 2000 ppm (Table 1) during the premating period were not considered to be treatment related. No adverse effects of treatment on body weight (data not shown) or body weight gain were noted in females during gestation (Table 2) or lactation (Table 3).

Food Consumption: A summary of food consumption data from selected time intervals is presented in Table 4. Transient decreases in food consumption were noted in the F_0 males and females and F_1 males fed diets containing 2000 ppm of the test material during the premating period. Detailed results are presented in the text.

A significant decrease in mean food consumption of F_0 males receiving 2000 ppm during week 1 of the premating period was noted; however, the study author suggested that this was most likely due to the nonpalatability of the test material. In the high-dose F_0 females, a significant decrease in food consumption was observed during the first 4 weeks of treatment. Mean food consumption in the high-dose F_1 males was significantly ($p<0.05$) lower than controls at weeks 3-4 and 6-7 of the 10-week premating and postmating (weeks 15-16) periods. No significant reductions in food consumption were seen in the low-, mid, and high-dose F_1 females during premating (data not shown).

Gestational and lactational food consumption in the treated F_0 females was similar to that of controls (data not shown). Mean food consumption in the high-dose adult F_1 females was significantly

($p<0.05$) reduced during gestation days 7-11 and 14-17 (data not shown). There was no effect of treatment on lactational food consumption in the F_1 females.

Compound Consumption: Mean compound consumption at 300, 1000, and 2000 ppm during the premating period was 20.7, 68.2, and 134.7 mg/kg/day, respectively, for F_0 males (data not shown) and 25.5, 81.3, and 164.7 mg/kg/day, respectively, for F_0 females (data not shown).

Mean compound consumption at 300, 1000, and 2000 ppm during the premating and postmating periods was 19.1, 62.5, and 125.4 mg/kg/day, respectively, for F_1 males (data not shown) and 24.8, 78.5, and 157.1 mg/kg/day, respectively, during premating for F_1 females (data not shown).

Compound consumption data for F_0 and F_1 females during gestation and lactation were not reported.

3. Reproductive Toxicity

The effects of dietary administration of the test material on reproductive parameters are summarized in Tables 5 and 6. Compound-related reproductive toxicity was observed at 2000 ppm. In both generations, the mean pup body weights at 2000 ppm were significantly reduced during the lactation and/or postweaning periods, suggesting a possible adverse effect on pup growth. No treatment-related effects on gestational length, mating, fertility, or gestational indices were observed.

In the F_1 generation offspring, there were no treatment-related effects on the total number of pups born, litter viability, live birth and survival indices, or sex ratios of pups (Table 5). There was also no effect of treatment on litter size (data not shown). Mean body weights of pups were significantly ($p<0.01$) decreased at 2000 ppm on lactational days 21 (by sex and combined for both sexes; Table 5 summarizes data for entire litters) and 28 (for females and entire litters; data not shown). Mean body weight gains of pups were significantly ($p\leq0.05$) reduced at 2000 ppm on lactational days 14-21 (males, females, and all pups) and 21-28 (females only) (data not shown). The gross and microscopic examination of selected weanling rats revealed no treatment-related lesions.

In the F_2 generation, no treatment-related adverse effects were noted on total number of pups born, litter viability, live birth and survival indices, or sex ratios of pups (Table 6). There was also no effect of treatment on litter size (data not shown). Mean body weights of pups (for each sex and for both sexes combined) were significantly ($p<0.01$) reduced at 2000 ppm on lactational day 28 and 1 week after weaning (data not shown). The gross and microscopic examination of selected weanling rats revealed no treatment-related lesions.

Table 1: Summary of Mean Body Weight Gain During the Premating Period for Rats Fed ADBAC for Two Successive Generations[a]

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Dietary Concentration (ppm)	Mean Body Weight Gain (g ± SD) for Study Weeks:			
	0-1	4-5	8-9	9-10
F_0 Males				
0	53.1 ± 3.9	25.4 ± 5.4	19.8 ± 4.9	13.0 ± 3.6
300	54.7 ± 5.1	27.9 ± 6.6	20.6 ± 10.4	12.7 ± 5.4
1000	56.0* ± 4.7	24.2 ± 5.3	16.2 ± 7.3	11.0 ± 5.0
2000	49.4 ± 7.2	20.5** ± 6.3	15.8 ± 7.3	11.3 ± 6.9
F_0 Females				
0	21.4 ± 5.9	7.9 ± 5.8	8.7 ± 4.2	3.1 ± 5.9
300	20.9 ± 6.9	13.6** ± 4.8	8.2 ± 5.8	6.8 ± 5.4
1000	24.7 ± 5.4	11.0 ± 6.0	5.7 ± 7.3	3.2 ± 6.80
2000	20.5 ± 7.0	6.0 ± 6.5	3.3** ± 4.3	0.5 ± 13.10
F_1 Males				
0	46.9 ± 5.2	21.0 ± 6.2	15.7 ± 6.0	9.4 ± 4.3
300	47.9 ± 6.2	22.1 ± 6.3	17.8 ± 7.2	11.8 ± 5.7
1000	58.3 ± 39.0	24.0 ± 4.5	17.1 ± 6.1	9.2 ± 4.7
2000	45.3 ± 5.8	20.0 ± 6.4	15.1 ± 5.9	8.4 ± 6.0
F_1 Females				
0	18.2 ± 4.5	5.6 ± 5.7	6.8 ± 7.7	2.6 ± 6.3
300	18.7 ± 6.4	5.3 ± 5.0	6.1 ± 6.5	2.1 ± 5.2
1000	20.6 ± 6.9	4.2 ± 6.3	6.6 ± 7.9	2.0 ± 5.5
2000	17.7 ± 4.6	3.0 ± 5.7	5.7 ± 6.3	0.8 ± 5.8

[a]Data extracted from study no. 52-524, Tables 5, 7, 24, and 26.

*Significantly differently from controls ($p<0.05$)
**Significantly differently from controls ($p<0.01$)

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Table 2. Summary of Mean Maternal Body Weight Gain During Gestation in Rats Fed ADBAC for Two Successive Generations[a]

Dietary Concentration (ppm)	Mean Body Weight Gain (g ± SD) for Gestation Days:			
	0-6	6-15	15-20	0-20
F_0 Females				
0	23.2 ± 5.3	35.0 ± 6.2	61.0 ± 11.3	120.0 ± 17.0
300	22.7 ± 4.1	34.3 ± 5.9	60.5 ± 10.4	117.8 ± 14.2
1000	26.8 ± 5.4	35.8 ± 6.4	62.3 ± 11.8	124.2 ± 18.5
2000	22.1 ± 15.0	39.4 ± 12.4	58.0 ± 8.8	119.9 ± 13.9
F_1 Females				
0	25.1 ± 6.1	33.9 ± 6.9	59.9 ± 13.5	118.9 ± 19.7
300	25.0 ± 6.0	30.9 ± 8.5	56.2 ± 12.8	112.2 ± 21.3
1000	24.8 ± 6.7	34.6 ± 6.6	59.8 ± 12.0	119.2 ± 16.6
2000	26.2 ± 6.8	34.4 ± 5.5	60.6 ± 9.1	121.08 ± 15.0

[a]Data extracted from study no. 52-524, Tables 13 and 32.

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Table 3. Summary of Mean Maternal Body Weight Gain During Lactation in Rats Fed ADBAC for Two Successive Generations[a]

Dietary Concentration (ppm)	Mean Body Weight Gain (g ± SD) for Lactation Days:			
	0-7	7-14	14-21	0-21
F_0 Females				
0	10.8 ± 13.9	11.9 ± 7.9	-9.1 ± 9.9	13.6 ± 17.3
300	8.6 ± 11.1	14.7 ± 6.7	-13.2 ± 6.5	10.1 ± 16.1
1000	12.0 ± 10.3	17.0 ± 9.3	-7.8 ± 10.5	21.1 ± 18.3
2000	23.5°° ± 12.3	18.3° ± 8.9	3.3°° ± 10.2	45.0°° ± 15.2
F_1 Females				
0	13.2 ± 13.2	14.1 ± 11.1	4.9 ± 11.4	32.1 ± 14.2
300	8.7 ± 11.2	11.3 ± 13.1	2.6 ± 13.5	22.5 ± 15.5
1000	16.2 ± 20.6	16.9 ± 10 5	-2.9 ± 14.6	30.2 ± 25.4
2000	17.3 ± 11.4	13.8 ± 11.7	12.1 ± 16.3	43.2 ± 17.8

[a]Data extracted from study no. 52-524, Tables 15 and 34.

°Significantly different from controls ($p<0.05$).
°°Significantly different from controls ($p<0.01$)

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Table 4. Summary of Mean Food Consumption (g/day ± SD) During the Premating Period in Rats Fed ADBAC for Two Successive Generations[a]

Dietary Concentration (ppm)	Mean Food Consumption (g/day ± SD) on Study Weeks:			
	0-1	3-4	4-5	9-10
F_0 Males				
0	24.2 ± 1.5	25.5 ± 1.5	25.4 ± 1.7	25.7 ± 1.8
300	24.7 ± 1.8	25.8 ± 2.3	26.2 ± 2.6	26.5 ± 2.3
1000	24.7 ± 1.4	26.1 ± 1.7	25.8 ± 1.7	26.3 ± 1.5
2000	22.3** ± 2.0	24.9 ± 2.2	24.6 ± 2.2	24.3 ± 2.9
F_0 Females				
0	17.5 ± 1.3	17.9 ± 1.4	17.5 ± 1.4	18.0 ± 1.3
300	17.2 ± 1.0	17.6 ± 1.2	18.6* ± 1.3	18.6 ± 1.2
1000	17.0 ± 0.9	17.3 ± 1.6	17.7 ± 1.6	17.5 ± 1.2
2000	15.9** ± 1.3	16.8* ± 1.6	17.1 ± 2.1	17.2 ± 2.1
F_1 Males				
0	26.1 ± 2.4	28.9 ± 3.0	28.2 ± 2.7	28.1 ± 2.4
300	27.2 ± 2.1	30.0 ± 2.3	29.9 ± 2.6	29.4 ± 2.4
1000	27.1 ± 2.1	29.6 ± 2.8	29.3 ± 2.5	28.9 ± 2.6
2000	25.4 ± 2.4	27.0* ± 3.2	26.9 ± 3.3	26.9 ± 2.6
F_1 Females				
0	18.4 ± 1.0	19.8 ± 1.3	19.7 ± 1.3	19.0 ± 1.6
300	19.0 ± 1.9	20.9 ± 2.2	20.6 ± 2.1	20.6* ± 1.8
1000	19.3 ± 2.4	20.6 ± 2.5	20.1 ± 2.6	20.2 ± 2.2
2000	17.9 ± 1.8	19.3 ± 1.8	19.1 ± 1.8	18.8 ± 2.0

[a]Data extracted from study no. 52-524, Tables 8, 10, 27 and 29.

*Significantly different from controls ($p<0.05$)
**Significantly different from controls ($p<0.01$)

Table 5. Summary of Effects of Dietary Administration of ADBAC on F_0 Reproductive Parameters, Offspring Survival, and Pup Body Weight[a]

Parameter	Dietary Concentration (ppm) 0	300	1000	2000
No. matings (F_0 parents)	28	28	28	28
No. pregnancies	28	27	28	27
Fertility index--female (%)[b]	100	96.4	100	96.4
Gestation index[c]	100	100	100	100
Mean gestation length (days)	22.0	22.0	22.0	22.0
Total no. live pups				
Day 0	366	335	371	343
Day 4 precull	359	330	362	339
Day 21	216	213	220	214
Mean no. live pups/litter[d]				
Day 0	13.1	12.4	13.3	12.7
Day 4 precull	12.8	12.2	12.9	12.6
Day 21	7.7	7.9	7.9	7.9
Live birth index (%)[e]	97.6	96.7	99.1	99.1
Viability index (%)[f]	99.6	100	100	100
Lactation index (%)[g]	99.1	100	100	100
Mean pup body weight (g)				
Day 1	6.8	6.9	6.9	6.8
Day 4 precull	9.9	10.2	10.1	10.0
Day 14	34.0	34.5	34.4	33.3
Day 21	54.8	55.2	55.3	51.5*
Sex ratio (% males)[h]	49.9	49.4	50.3	52.7

[a]Data were extracted from study no. 52-524, Tables 12, 17, 18, 19 and 20.

[b]$\frac{\text{No. of females bearing litters}}{\text{No. of females copulating}} \times 100$

[c]$\frac{\text{No. of litters with at least one live pup}}{\text{No. of litters}} \times 100$

[d]Mean number of implantations/dam was not reported.

[e]$\frac{\text{No. of pups born alive}}{\text{No. of pups born}} \times 100$

[f]$\frac{\text{No. of pups alive on day 28}}{\text{No. of pups alive at day 21}} \times 100$

[g]$\frac{\text{No. of pups alive on day 21}}{\text{No. of pups alive on day 4}} \times 100$

[h]Sex ratio on lactation day 0

*Significantly different from controls ($p<0.01$)

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Table 6. Summary of Effects of Dietary Administration of ADBAC on F_1 Reproductive Parameters, Offspring Survival, and Pup Body Weight[a]

Parameter	Dietary Concentration (ppm) 0	300	1000	2000
No. matings (F_0 parents)	27	27	28	28
No. pregnancies	25	24	23	25
Fertility index--female (%)[b]	92.6	96.0	85.2	96.2
Gestation index[c]	100	100	100	100
Mean gestation length (days)	21.9	22.0	22.1	21.9
Total no. of live pups				
Day 0	327	295	305	336
Day 4 precull	321	285	301	324
Day 21	189	173	179	197
Mean no. live pups/litter[d]				
Day 0	13.1	12.3	13.3	13.4
Day 4 precull	12.8	11.9	13.1	13.0
Day 21	7.6	7.2	7.8	7.9
Live birth index (%)[e]	98.6	97.8	99.5	97.4
Viability index (%)[f]	100	100	100	100
Lactation index (%)[g]	99.5	99.5	100	99.5
Mean pup body weight (g)				
Day 1	6.7	6.8	6.9	6.7
Day 4 precull	9.7	9.8	10.2	9.9
Day 14	30.3	29.4	30.9	30.0
Day 21	47.8	46.7	48.8	45.4
Sex ratio (% males)[h]	50.7	46.7	47.9	51.8

[a]Data were extracted from study no. 52-524, Tables 31, 36, 37, 38, and 39.

[b]$\frac{\text{No. of females bearing litters}}{\text{No. of females copulating}} \times 100$

[c]$\frac{\text{No. of litters with at least one live pup}}{\text{No. of litters}} \times 100$

[d]Mean number of implantations/dam was not reported.

[e]$\frac{\text{No. of pups born alive}}{\text{No. of pups born}} \times 100$

[f]$\frac{\text{No. of pups alive on day 21}}{\text{No. of pups alive at day 21}} \times 100$

[g]$\frac{\text{No. of pups alive on day 21}}{\text{No. of pups alive on day 4}} \times 100$

[h]Sex ratio on lactation day 0

Gross and Microscopic Pathology: No treatment-related gross or microscopic changes were observed in either F_0 or F_1 adult male or female rats at any dose level.

D. REVIEWERS' DISCUSSION/CONCLUSIONS

1. Test Material Analyses

No information was provided to support the study author's claim that the test material was 81.09% pure. The concentrations of the test material in the diet were within the acceptable range (±10% of nominal values). The results of homogeneity analyses indicated that the test material was homogeneously distributed in the test diets. Results of the stability analyses indicated that the test material in the diet was stable for up to 21 days when stored at room temperature.

2. Parental Toxicity

There was no definitive evidence of compound-related toxicity at 2000 ppm, Although the study authors thought there was an effect on mean body weight at 2000 ppm. BAD 4/15/93 Mean body weight was significantly lower in the adult F_0 females receiving 2000 ppm during weeks 5, 6, 9, and 10 of the premating period. Mean body weight gain in these females was also significantly lower during weeks 8-9 of the premating period. Food consumption was decreased in the adult F_0 females only during the first 4 weeks of treatment. However, since test material palatability was a problem and the significant weight differences noted for weeks 5, 6, 9, and 10 were discreet (i.e., 4.5% lower than control), the findings did not provide clear evidence of an adverse effect on female body weight. Decreases in mean body weight gains and food consumption for adult F_1 males receiving 2000 ppm during the premating period were transient, lasting 1-2 weeks.

No treatment-related mortality or clinical signs of toxicity were observed in either generation at any dose level during the treatment period.

Based on these results, the NOEL for parental toxicity was 2000 ppm; the LOEL was not established.

3. Reproductive Toxicity

Compound-related reproductive toxicity was observed at 2000 ppm.

As also noted by the study authors, BAD 4/15/93 reductions in mean body weights and/or mean body weight gains were noted in F_1 and F_2 pups at 2000 ppm during lactation. Mean body weights of F_1 pups were decreased on lactational days 21 (for both sexes and entire litter) and 28 (for females and entire litter). Mean body weight gain of F_1 pups was decreased on lactational days 14-21 (males, females, and all pups) and 21-28 (females only). Mean body weights of F_2 pups (males, females, and all pups) were decreased on lactational day 28. There were no treatment-related effects on other reproductive end points. (See Appended Tables 19 and 38 from the study.) BAD 4/15/93

Based on these results, the NOEL and LOEL for reproductive toxicity were 1000 and 2000 ppm, respectively.

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4. Study Deficiencies

(a) The purity of the test material was reported but not verified by a signed analysis statement from the sponsor. BaD 4/11/93

(b) Maternal signs of toxicity noted at the high dose were limited to decreases in mean body weight and body weight gain of the F_0 females during the premating period. Although the decreases in body weight and body weight gain values during the premating period were reported to be statistically significant, there were overlaps of confidence intervals for body weight values between the high-dose F_0 and control females. Consequently, no LOEL for parental toxicity was established.

E. CORE CLASSIFICATION: Core ~~Minimum~~ Guideline Data

Parental Toxicity NOEL = 2000 ppm (146 mg/kg/day) male ; female ; high dose ; combined

Parental Toxicity LOEL = Not determined

Reproductive Toxicity NOEL = 1000 ppm (73 mg/kg/day) male ; female high dose combined

Reproductive Toxicity LOEL = 2000 ppm (146 mg/kg/day) male ; female high dose combined based on reductions in pup body weight and body weight gain during lactation

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