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

Microfiche

OCT 27 1992

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OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Ethylene thiourea (ETU-443AA)
Tox. Data Submitted from Rat Reproduction Study, Under MRID 42391701 and 42391801.
ID #014504

Chemical: 913A (443AA)
RD Record: S-422030
HED Project: D180741

FROM: Irving Mauer, Ph.D., Geneticist
Toxicology Branch-I
Health Effects Division (H7509C)

10/15/92

TO: Walter Waldrop/Terri Stowe (PM #71)
Reregistration Branch
Special Review and Reregistration Division (H7508W)

THRU: Karl P. Baetcke, Ph.D., Chief
Toxicology Branch-I
Health Effects Division (H7509C)

10/23/92

Registrant: ETU Task Force (Rohm and Haas, Dupont, BASF, Pennwalt)

Request: Review and evaluate the following toxicity study:

(83-4) Two Generation Reproduction Study with Ethylene Thiourea (ETU) in the Rat, performed by RCC, Research and Consulting Company, AG, Itingen, Switzerland, RCC Study # 252300, Final Report dated January 15, 1992 (MRID 42391701 and 42391801).

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TOXICOLOGY BRANCH CONCLUSIONS: In addition to other major deficiencies, the investigators were unable to determine NOELs or LOELs for either parental or reproductive toxicity (see attached DER). Hence the study is considered INVALID for regulatory purposes, and must be repeated to satisfy Guideline 83-4.

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2ATTACHMENT (Data Evaluation Record)

DOC 930209

FINAL

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DATA EVALUATION REPORT

ETHYLENE THIOUREA

Study Type: Reproductive Toxicity

Prepared for:

Health Effects Division
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

Principal Reviewer: Sanju Diwan, Ph.D. Date 10/5/92

Co-Principal Reviewer: Patricia Bittner, M.S. Date 10/5/92

Independent Reviewer: Pia Lindstrom, DPH Date Oct. 1992

QA/QC Manager: Sharon Segal, Ph.D. Date 10/5/92

Contract Number: 68D10075
Work Assignment Number: 1-135
Clement Number: 93-134
Project Officer: James Scott

Guideline Series 83-4: Reproductive Toxicity

EPA Reviewer: Irving Mauer, Ph.D.
Insect/Rodent., Toxicology Branch I/HED
Signature: [signature]
Date: 10-13-92

EPA Branch Chief: Karl Baetcke, Ph.D.
Toxicology Branch I/HED
Signature: _____
Date: _____

DATA EVALUATION REPORT 009806

STUDY TYPE: Reproductive toxicity

EPA IDENTIFICATION NUMBERS

TOX CHEM. No.: 913A (443AA)/014504

MRID NO.: 423917-01

RCC PROJECT NUMBER: 252360

TEST MATERIAL: Ethylene thiourea

SYNONYMS: 2-imidazolidinethione, ETU, imidizoline-2-thiol, 2-mercaptoimidizoline, Akrochem ETU-22, Robac 22, Sanceller 22, NA-22, Vulkacit NVP/C

SPONSOR: ETU Task Force (Rohm and Haas, DuPont, BASF, Pennwalt)

STUDY NUMBER: 252360

TESTING FACILITY: RCC, Research and Consulting Co., AG, Itingen, Switzerland

TITLE OF REPORT: Two-generation Reproduction Study with Ethylene Thiourea (ETU) in the Rat

AUTHORS: A. Dotti, J. Kinder, J. Wright

REPORT ISSUED: January 15, 1992

CONCLUSIONS: In a two-generation reproduction study, Sprague-Dawley rats were fed ethylene thiourea (ETU) in the diet at dosage levels of 0, 2.5, 25, or 125 ppm. Based on the study authors' analyses, compound-related effects were observed in both sexes and generations at 25 and 125 ppm as evidenced by histopathological findings in the thyroid and pituitary. The reviewers have not determined a NOEL/LOEL for parental toxicity because of inconsistencies in concentration, stability and homogeneity of the test material in the diet and variability in the data regarding food and test material consumption (see Study Reporting Deficiencies below for further details).

According to the study authors' analyses, no adverse effects were observed in the reproductive parameters measured. The reviewers have not determined a NOEL/LOEL for reproductive toxicity because of the incomplete data set due to missing pups in all dosage groups (see Study Reporting Deficiencies below for further details).

CLASSIFICATION: Invalid Data. This study does not meet the requirements set forth under Guideline Series 83-4 for a two-generation reproductive toxicity study in rats. Dams did not receive the appropriate test concentrations as indicated by the analytical chemistry data and a high number of 'missing' pups was not accounted for, indicating that GLPs may not have been practiced.

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A. MATERIALS

Test Compound

Purity:	98%
Description:	White powder
Batch no.:	Aldrich Lot No. 02506EV
Received:	Not reported
Contaminants:	Not reported
Storage conditions:	Stored at 4°C; protected from light and moisture

Vehicle: None used; the test material was administered in the diet.

Test Animals

Species:	Rat
Strain:	Sprague-Dawley [IcoIbm: OFA (SPF)]
Source:	BRL, Biological Research Laboratories, Ltd., Fullinsdorf, Switzerland
Age:	4 weeks
Weight:	F_0 males--131-179 g on study day 1 F_0 females--89-130 g on study day 1

B. STUDY DESIGN

This study was designed to assess the potential of ETU to cause reproductive toxicity in rats when administered in the diet for two successive generations.

Mating: After 10 days of acclimatization followed by 70 days of dietary treatment, the F_0 females were mated with males from the same group in a ratio of 1:1 until evidence of mating was obtained (presence of sperm in daily vaginal smear and/or appearance of vaginal plug) or for a maximum of 19 days. The day on which mating was confirmed was designated gestation day (GD) 0. The F_1 animals were mated in a similar fashion following 126 days of exposure to the test compound. Sibling matings were avoided. Females not showing evidence of mating after 21 days of pairing were paired with different males until mating occurred or for a maximum of 14 days.

Animal Husbandry: Prior to mating, animals were housed individually in Makralon type-3 cages. Food (powdered standard Kliba 343, Klingentalmuehle, Kaiseraugst, Switzerland) and tap water were available ad libitum. Both the diet and water were analyzed for contaminants. The animal room was air-conditioned with 10-15 air changes per hour and a temperature of 19-25°C. Relative humidity was 40-70%, and a 12-hour light/dark cycle was maintained.

Group Arrangement: F_0 animals were assigned to groups using computer-generated randomization, and F_1 animals were randomly (method not specified) distributed as follows.

Test Group	Dietary Level (ppm)	Number Assigned per Group F_0 Males	F_0 Females	F_1 Males	F_1 Females
Control	0	25	25	25	25
Low dose	2.5	25	25	25	25
Mid dose	25	25	25	25	25
High dose	125	25	25	25	25

Dosage Administered: The test material was administered continuously in the diet for two successive generations. Test diets were prepared weekly. A pre-mix was first prepared by mixing the test compound with the basal diet for an unspecified time in a Braun® mixer. A small amount of diet was added to this original mixture and blended for an unspecified time in a Rotel® mixer. More feed was then added to achieve the desired concentration; the mix was blended once again for 10 minutes in an Oertli® mixer. This gave the final diet concentration for high-dosage animals. The low- and mid-dosage diets were prepared by further addition of basal diet into the high-dosage stock diet. Diets were stored at room temperature in paper bags.

The homogeneity and stability of the test diet were determined before the initiation of this study for a chronic toxicity study (RCC Project 256803). However, no results were provided with this study. Homogeneity was measured for one batch of pretest diet. Analysis of the diet samples used in this study was performed by Enviro-Biotech, Inc., using gas chromatography. Feed was sampled and shipped frozen to the laboratory until analyzed. Stability and dosage concentration were measured in feed prepared during study weeks 1, 2, 6, 10, 14, 18, 22, and 26. Further samples were taken monthly from feed prepared through the end of the study and were stored frozen at RCC. However, they were not analyzed.

Dosage Rationale: The dosage levels were selected by the sponsor and based primarily on thyroid toxicity; no details of the earlier study were provided.

Observations: Observations for mortality, moribundity, and overt signs of toxicity were conducted twice a day. Physical examinations were performed weekly. Body weights for all animals were determined weekly prior to mating. Male body weights were recorded weekly for the duration of the study; mated females were weighed on GDs 0, 7, 14, and 21 and on lactation days 1, 4, 7, 14, and 21. Food consumption was recorded weekly for all animals during the premating, gestation, and lactation periods. Females were examined twice daily for signs of parturition toward the end of their gestation period, and length of gestation was calculated.

The following data were recorded for each litter:

- Litter size (live and stillborn pups)
- Sex of pups on lactation days 0, 4, and 21
- Daily nursing behavior and nesting activity
- Gross physical anomalies
- Individual pup body weight on lactation days 0 (if possible), 1, 4, 7, 14, and 21

On lactation day 4, F_1 pups were randomly culled to four/sex/litter. Excess pups were sacrificed, examined macroscopically, and preserved. F_1 pups were weaned on day 21, and 25 male and 25 female pups were randomly selected as F_1 parental animals. F_2 pups were culled, examined, and preserved in a similar manner. All dead pups from both generations were necropsied and/or preserved unless excessively cannibalized. F_2 pups and F_1 parents were sacrificed and necropsied on day 21 post partum. All F_0 and F_1 animals, including those found dead, were necropsied. Animals were killed by an intraperitoneal injection of sodium pentobarbital and exsanguination. For all F_0 animals and all F_1 parent animals, the following organs and tissues were preserved in neutral phosphate buffered 4% formaldehyde solution:

- gross lesions
- liver
- ovaries
- pituitary gland
- prostate
- seminal vesicles
- thyroid with parathyroid
- testes with epididymis
- uterus and cervix
- vagina

In addition, the pregnancy status of each apparently nonpregnant female was confirmed by staining the uterus with ammonium sulfide for accentuation of the implantation sites.

Histopathological examinations were performed on the organs and tissues listed above from all F_0 and F_1 high-dosage and control animals selected for mating, and from animals killed in extremis and animals that died during the study. Additionally, the following organs were examined histologically:

- pituitary and thyroid glands from all F_0 and F_1 animals in the low and mid-dose groups
- reproductive organs of all infertile males and female F_0 and F_1 animals (all groups)
- those with macroscopic abnormalities from all animals in all generations (F_0 and F_1 parent animals)

Statistical Analysis: The following analyses were conducted of body weights, food consumption, and reproduction and histopathology data.

- Intergroup differences were evaluated using univariate one-way analysis of variance.

- Intergroup comparisons were conducted using the Dunnett t-test.

- The spontaneous pup mortality data were analyzed using Fisher's Exact test.

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Compliance:

- A signed Statement of No Data Confidentiality Claim, dated January 30, 1992, was provided.

- A signed Statement of Compliance with EPA, OECD, and Japanese GLPs, dated January 15 and 30, 1992, and March 24, 1992, was provided.

- A signed Quality Assurance Statement, dated January 17, 1992, was provided.

C. RESULTS

Test Material Analysis Analyses of pretest diet for homogeneity and study test diets for stability and dosage concentration revealed values outside acceptable ranges. Homogeneity analysis (of the top, middle, and bottom portions of samples) revealed concentrations from 64% to 152% of target, with 10/18 samples outside acceptable limits. Stability and dosage concentration analyses were conducted together; the concentrations of the test material in the diet ranged from 23% to 221% of target, with only 8/42 samples containing test material within ±10% of acceptable values. Four samples were retested, and all four were found to be outside acceptable limits. Although fluctuations were present in all sample groups, decreases in percent recovery were particularly striking during weeks 18-26 in the high-dosage diet, with 5/6 samples showing recoveries of 23-39%. During analyses of the test diets, the study authors noted wide variations in the recovery and an inconsistency in the results of the duplicate analysis.

Parental Toxicity

Mortality/moribundity: No mortality considered by the authors to be treatment-related was observed.

In F_1 animals, one low-dosage female was found dead on day 20 of mating. Necropsy revealed foci on the exorbital lacrimal glands and thymus, and reddish discoloration of several organs including the pancreas, salivary glands, lungs, ovaries, and mandibular lymph node. One mid-dosage female was found dead on day 19 of post-mating after exhibiting vaginal bleeding, ruffled fur, and dyspnea. Necropsy revealed foci on the thymus, liver, and stomach as well as discoloration and enlargement of lymph nodes. One high-dosage female was killed in extremis on day 124 during mating and had a mammary adenocarcinoma. One mid-dosage male was killed in extremis on postmating day 12; necropsy revealed urogenital inflammation.

Clinical Observations: Possible compound-related effects were observed in F_1 rats and included vaginal bleeding in one mid-dosage female and a mass under the right foreleg in another, which was later diagnosed as

mammary adenocarcinoma. In addition, two high-dosage F_1 females had lesions either in the vagina or in the cervical region, and in addition, one of these females had a mammary adenocarcinoma. These lesions were not found in controls, and therefore, may have been treatment related. However, because of lack of data on the incidence of these tumors in the historical controls, this finding could not be confirmed. One high-dosage male had a mass (which disappeared at a later stage) on the left corner of the mouth .

Body Weight: Compound-related effects in body weight and body weight gain were observed only in F_0 high-dosage males. Summaries of body weight gain from selected time intervals are presented in Table 1.

Among F_0 males during premating, body weight at the highest dosage (data not shown) decreased significantly from day 22 to 70 ($\geq$4%; $p \leq 0.01$) compared to control. These males also had decreased body weight during the first week of the postmating period. The percent body weight gain from day 1, on the other hand, was significantly lower (7%) only from days 15 to 22 and 22 to 29 of premating, and on day 15 of the postmating period. Significant increases in body weight gains of F_0 males at all three dosage levels during postmating, and in body weight of F_1 males of the low- and mid-dosage levels during premating were not considered to be treatment related.

Food Consumption: No conclusions can be drawn regarding the effects of the compound on food consumption. Relative food consumption was lower in all dosage groups among males of both generations beginning on day 43 until the end of the premating period. A summary of relative mean food consumption (g/kg/day) from selected time intervals during the premating period is presented in Table 3. The relative food consumption was calculated as a mean value by the study authors. However, because of the severe spillage of food at frequent intervals by males and females of both generations, they suggested that these figures were artificially high. Therefore, they considered the minimum values to represent the actual food consumption. The reviewers, however, believe that the effects of the test material on food consumption cannot be adequately assessed when using such methodology.

Compound Intake: Because of the frequent spillage of diet, no definitive assessment of the actual compound intake by the animals can be made. The mean values for the test material intake for all animals were calculated based on food consumption and body weight determinations. Intake values were not adjusted and analyzed for test material concentrations.

Gross and Microscopic Pathology: No compound-related gross findings in parental animals were observed. Incidental findings included dilation of the renal pelvis, renal calculi, flaccid testes, watery fluid in the testes, dilation of the uterine horns, ovarian cyst, malformation of liver lobules, and diaphragmatic hernia.

Compound-related microscopic changes were observed in the anterior pituitary and thyroid glands at 25 and 125 ppm. A summary of these effects is presented in Table 4.

Increased incidences of histopathologic lesions in both sexes and generations were observed at 25 and 125 ppm and included primary lesions in the anterior pituitary and thyroid glands. Among F_0 high-dosage animals, there were significant increases in the incidences of anterior pituitary cell hypertrophy, thyroid follicular cell hypertrophy, and thyroid follicular cell hyperplasia compared to controls. Among F_1 animals, there were significant increases in the incidences of anterior pituitary cell hypertrophy (high-dosage males and females), thyroid follicular cell hyperplasia (mid-dosage males, high-dosage males and females), follicular cell hypertrophy (high-dosage males and females) and increased incidence of reduced colloid in the thyroid (high-dosage males and females). Histopathology also revealed an increased incidence of follicular adenoma in three high-dosage F_1 males, compared to none in controls (data not shown). The significant increases in the incidences of mononuclear cell infiltration in the kidney and prostate in F_1 males were considered to be incidental (data not shown).

Reproductive Toxicity

No compound-related effects were observed on male or female fertility indices, length of gestation, pup/sex ratio, litter size, or body weights during lactation for any generation or dosage group. Summaries of results for reproduction parameters are presented in Tables 5 and 6.

In the F_0 generation at 125 ppm, the mean number of implantations increased significantly (data not shown). In addition , at 2.5 ppm a slight increase in the mean number of implantations coupled with lower postimplantation loss, resulted in a significant increase in the mean number of live pups (data not shown). The above findings were considered to be incidental.

During the postnatal period, the increase in the number of dead pups of both generations (Tables 5 and 6) was possibly caused by the failure of dams to nurse their pups since no clinical findings were noted in these pups. This effect was seen in all dosage groups (including controls) and, therefore, was not considered to be compound related. Many pups were missing during lactation days 0-21 (Tables 5 and 6), which resulted in a reporting deficiency and an incomplete data set. The survival and lactation indices calculated by the reviewers and reported in Tables 5 and 6 exclude the pups from all dosage groups that were missing throughout lactation.

C. REVIEWERS' DISCUSSION/CONCLUSIONS

Test Material Analyses: The purity of the compound was 98%. The stability and homogeneity of the test material in the diet were outside the acceptable range of ±10% of nominal; the concentrations were outside the acceptable range of ±20% of nominal.

Parental Toxicity: Based on the study authors' analyses of the data, compound-related effects were observed at 25 and 125 ppm in both sexes and generations. They were manifested as significantly decreased body weight/weight gain in the F_0 males (125 ppm) and an increased incidence

of lesions in the thyroid and anterior pituitary glands (25 and 125 ppm) in both sexes and generations.

The reviewers have not determined either a NOEL or a LOEL for parental toxicity because excessive spillage prevented adequate quantification of the food and test material consumption, and because there was a lack of consistent dosage concentration data.

Reproductive Toxicity: Based on the study authors' analyses, no reproductive toxicity was observed at the dosages tested. The reviewers have not determined either a NOEL or a LOEL for reproductive toxicity because of the lack of consistent test material intake and low F_2 pup viability in all dosage groups as well as high numbers of missing pups that were unaccounted for in all dosage groups.

Study/Reporting Deficiencies: A major problem is believed to exist with the stability, homogeneity, and concentrations of the test compound in the diet. Although a Data Evaluation Report has been prepared based upon the study authors' analyses, the reviewers believe that the conclusions drawn from the results are invalid owing to the following deficiencies:

- Stability, homogeneity, and concentration analyses indicated that the values were outside the acceptable limits and further suggests that the animals did not receive the target concentrations. In addition, no explanation was provided as to why the samples were obtained but were not analyzed for stability and concentrations for up to 3 months, or why analysis was not performed for samples prepared on or after June 1, 1990, through termination (October, 1990).

- Storage conditions are stated by the authors as "4°C, away from light and moisture" yet the test material in feed was stored at room temperature in paper bags.

- Because of frequent severe food spillage, no determination of the actual food consumption and test compound consumption by the animals could be made. For males of both generations, there was a drastic reduction in food consumption from day 43 until the end of the premating period, which was possibly caused by the nonpalatability of the diet and frequent spillage. The individual food consumption values varied widely within the groups (see Appendix, study pages 246 and 247).

- Mean values for test material intake were based on food consumption and body weight determinations. Intake values were not adjusted for analyzed test material concentrations.

- Body weight gain (%) varied widely for individual dams and pups within a given group or litter (see Appendix, study pages 299 and 317, respectively) and indicate that there may have been a problem with the balance in use.

- Several pups from all dosage groups died during the lactation period (days 1-21), and many were missing and unaccounted for, which resulted in an incomplete data set.

The above deficiencies indicate that the laboratory may not have complied with Good Laboratory Practice Standards and prevent valid conclusions to be drawn.

D. CLASSIFICATION: Invalid Data (because of several major deficiencies discussed above)

Parental Toxicity NOEL - Not determined
Parental Toxicity LOEL - Not determined

Reproductive Toxicity NOEL - Not determined
Reproductive Toxicity LOEL - Not determined

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E. RISK ASSESSMENT: Not applicable

Table 1. Mean Body Weight Gain (%) during the Premating Period for Rats Administered ETU in the Diet for Two Successive Generations[a]

Study Days:	Dosage Level (ppm) 0	2.5	25	125
F_0 Males				
1- 8	39.9 ± 4.9	42.6 ± 4.3	41.9 ± 4.1	39.0 ± 3.6
22-29	138.7 ± 12.5	144.9 ± 13.5	143.4 ± 11.5	129.0 ± 16.1*
43-50	195.0 ± 20.9	203.5 ± 22.8	199.9 ± 18.3	182.8 ± 26.1
64-70	228.3 ± 27.0	241.2 ± 28.7	232.8 ± 23.4	214.1 ± 31.0
F_0 Females				
1- 8	34.6 ± 6.5	35.8 ± 6.6	37.0 ± 7.1	33.6 ± 6.0
22-29	96.4 ± 13.9	100.6 ± 16.2	101.3 ± 18.6	93.3 ± 13.5
43-50	126.8 ± 19.3	134.9 ± 22.8	136.0 ± 23.6	126.2 ± 16.8
64-70	143.6 ± 19.4	154.8 ± 25.1	154.6 ± 26.9	143.2 ± 17.4
F_1 Males				
1- 8	49.0 ± 6.4	47.2 ± 5.6	46.4 ± 6.1	48.9 ± 5.5
22- 29	183.2 ± 28.9	177.2 ± 21.4	178.1 ± 33.3	181.7 ± 20.9
43- 50	257.9 ± 47.3	254.7 ± 34.0	253.8 ± 53.2	256.2 ± 34.8
64- 71	296.2 ± 58.0	296.2 ± 42.4	292.2 ± 56.5	298.6 ± 44.7
85- 92	334.4 ± 65.9	336.6 ± 53.5	327.6 ± 67.5	339.2 ± 46.3
106-113	356.9 ± 73.3	362.6 ± 59.1	355.4 ± 82.9	368.7 ± 52.0
120-126	370.0 ± 75.0	376.4 ± 63.1	369.6 ± 85.4	386.6 ± 54.7
F_1 Females				
1- 8	40.4 ± 8.1	35.9 ± 5.9	40.4 ± 6.6	40.0 ± 9.0
22- 29	115.6 ± 21.4	106.4 ± 15.0	116.2 ± 31.1	117.7 ± 22.7
43- 50	152.6 ± 27.0	140.9 ± 20.6	156.0 ± 43.5	159.7 ± 32.4
64- 71	170.2 ± 31.5	156.4 ± 24.0	175.9 ± 47.4	175.0 ± 35.9
85- 92	185.7 ± 34.3	172.1 ± 27.2	191.6 ± 55.1	192.3 ± 39.8
106-113	195.1 ± 34.0	185.1 ± 27.3	207.6 ± 58.1	206.7 ± 41.4
120-126	200.4 ± 35.9	187.7 ± 27.4	211.4 ± 60.2	213.4 ± 39.5

[a]Data were extracted from Study No. 252360, pp. 97, 166, 101-102, 172-173, 261-262, 265-268, 299-300, and 305-308.

*Significantly different from control ($p \leq 0.05$)

Table 2. Mean Body Weight Gain (%) during the Gestation Period for Rats Administered ETU in the Diet for Two Successive Generations[a]

Gestation Days:	Dosage Level (ppm) 0	2.5	25	125
F_0 Generation				
0- 7	12.6 ± 2.7[b]	11.8 ± 3.0	10.3 ± 2.4*	11.3 ± 2.8[c]
7-14	24.6 ± 3.4	23.9 ± 3.7	21.4 ± 3.8*	23.5 ± 4.4
14-21	59.5 ± 7.5	61.9 ± 5.9	56.9 ± 7.9	61.2 ± 8.0
F_1 Generation				
0- 7	11.2 ± 2.8	12.5 ± 2.6	10.9 ± 3.2	10.5 ± 2.4
7-14	20.1 ± 3.4	21.4 ± 3.4	19.6 ± 4.9	20.0 ± 2.9
14-21	50.9 ± 7.3	52.5 ± 8.7	53.2 ± 9.7	50.6 ± 7.4

[a]Data were extracted from Study No. 252360, pp. 168, 175, 301-302, and 309-310.

[b]Sample size N=24; one animal was not pregnant.

[c]Sample size N=23; four females were not pregnant.

*Significantly different from control ($p \leq 0.05$)

Table 3. Relative Mean Food Consumption (g/kg/day ± S.D.) during the Premating Period for Rats Administered ETU in the Diet for Two Successive Generations[a]

Gestation Days:	Dosage Level (ppm) 0	2.5	25	125
F_0 Males				
1- 2	169.2 ± 27.5	177.4 ± 21.5	188.5 ± 44.3	174.8 ± 38.6
8- 9	138.4 ± 18.4	141.1 ± 17.1	149.1 ± 21.7	139.3 ± 13.7
22- 23	102.4 ± 23.9	104.2 ± 14.0	113.2 ± 29.6	114.3 ± 48.8
29- 30	108.4 ± 62.3	99.0 ± 11.8	112.4 ± 28.0	99.9 ± 12.8
43- 44	93.8 ± 64.9	83.8 ± 11.1	95.6 ± 33.6	94.6 ± 24.8
50- 51	82.4 ± 30.4	91.6 ± 37.0	98.6 ± 66.2	94.8 ± 34.2
64- 65	91.0 ± 76.6	85.1 ± 26.9	99.3 ± 54.4	102.2 ± 48.2
69- 70	89.8 ± 67.3	81.7 ± 31.5	95.6 ± 62.5	98.2 ± 60.0
F_0 Females				
1- 2	184.8 ± 24.8	221.2 ± 158.6	216.0 ± 44.9	184.6 ± 19.6
8- 9	162.2 ± 28.4	186.6 ± 102.6	182.4 ± 55.5	162.0 ± 31.3
22- 23	128.4 ± 25.6	153.1 ± 50.9	180.1 ± 107.8*	137.0 ± 47.3
29- 30	117.9 ± 30.8	141.9 ± 40.3	156.8 ± 80.6*	121.5 ± 26.4
43- 44	108.4 ± 24.5	144.9 ± 68.5	170.9 ± 84.7**	112.3 ± 31.1
50- 51	111.4 ± 33.7	146.2 ± 81.1	195.5 ± 146.7**	129.1 ± 79.4
64- 65	123.0 ± 89.4	145.6 ± 80.7	182.2 ± 130.8	106.8 ± 26.5
69- 70	121.6 ± 68.0	145.1 ± 83.8	179.1 ± 123.3	126.2 ± 75.2
F_1 Males				
1- 2	206.4 ± 53.6	215.7 ± 53.4	195.4 ± 48.4	201.4 ± 56.1
8- 9	157.9 ± 18.4	197.6 ± 224.1	153.7 ± 32.2	158.8 ± 41.1
22- 23	122.4 ± 32.8	131.8 ± 60.0	131.9 ± 48.4	144.1 ± 119.6
29- 30	109.7 ± 26.4	114.3 ± 45.8	113.5 ± 37.9	99.8 ± 22.8
43- 44	93.1 ± 20.7	101.8 ± 36.9	105.7 ± 65.2	87.2 ± 32.9
50- 51	97.9 ± 27.4	106.9 ± 36.1	114.8 ± 80.5	99.7 ± 42.8
64- 65	87.7 ± 49.8	104.9 ± 44.8	109.7 ± 71.6	95.4 ± 54.5
71- 72	72.5 ± 9.9	83.7 ± 23.4	88.3 ± 27.0	81.5 ± 36.6
85- 86	81.0 ± 27.9	86.2 ± 25.3	96.7 ± 51.5	81.0 ± 31.3
92- 93	66.4 ± 18.9	76.5 ± 28.5	99.7 ± 77.5*	75.4 ± 29.6
106-107	71.0 ± 16.3	73.5 ± 19.5	72.4 ± 19.7	72.5 ± 32.3
113-114	79.6 ± 21.5	83.1 ± 33.6	87.3 ± 39.4	81.2 ± 41.4
125-126	71.3 ± 14.1	79.4 ± 34.7	84.4 ± 27.5	76.8 ± 34.7
F_1 Females				
1- 2	190.7 ± 27.6	198.0 ± 52.6	201.3 ± 70.7	260.9 ± 297.9
8- 9	163.7 ± 37.3	188.6 ± 62.0	194.2 ± 188.6	248.6 ± 305.5
22- 23	174.7 ± 74.2	182.6 ± 90.0	295.4 ± 215.1	266.7 ± 274.2
29- 30	133.6 ± 43.3	156.8 ± 126.4	164.9 ± 81.8	202.2 ± 233.1
43- 44	128.1 ± 51.1	156.8 ± 126.4	233.8 ± 182.1*	160.6 ± 157.8
50- 51	153.9 ± 65.4	168.1 ± 120.9	228.6 ± 163.2	192.0 ± 154.8
64- 65	138.1 ± 66.0	147.6 ± 92.4	176.3 ± 114.8	230.7 ± 184.1*
71- 72	119.1 ± 49.1	107.1 ± 37.0	119.3 ± 37.4	139.7 ± 107.5
85- 86	132.2 ± 54.6	128.8 ± 74.2	113.2 ± 53.2	119.3 ± 132.7
92- 93	101.4 ± 31.7	121.0 ± 64.3	136.4 ± 65.8	131.1 ± 88.0
106-107	105.7 ± 44.1	105.1 ± 33.6	134.5 ± 59.2	114.6 ± 92.1
113-114	156.2 ± 135.3	125.9 ± 73.3	172.6 ± 144.7	175.7 ± 178.5
125-126	145.6 ± 109.9	135.4 ± 73.5	173.2 ± 94.3	151.5 ± 92.6

[a]Data were extracted from Study No. 252360, pp. 73-74, 78-80, 134-135, and 141-143; individual data were not reported.

*Significantly different from control ($p \leq 0.05$)

**Significantly different from control ($p \leq 0.01$)

Table 4. Incidences of Histopathologic Findings in Rats Administered ETU in the Diet for Two Successive Generations[a]

Gestation Days:	Dosage Level (ppm) 0	2.5	25	125
No. animals examined	25	25	25	25
F_0 Generation--Males				
Anterior pituitary cell hypertrophy	16	17	21	24*
Thyroid,				
Follicular cell hyperplasia	1	0	5	23*
hypertrophy	1	0	0	15*
Reduced colloid	0	2	4	3
F_0 Generation--Females				
Anterior pituitary cell hypertrophy	0	0	0	20*
Thyroid,				
Follicular cell hyperplasia	0	0	1	17*
hypertrophy	0	0	3	19*
Reduced colloid	0	0	0	0
F_1 Generation--Males				
Anterior pituitary cell hypertrophy	11	16	15	25*
Thyroid,				
Follicular cell hyperplasia	0	0	6*	25*
hypertrophy	0	0	1	9*
Reduced colloid	0	0	1	6*
F_1 Generation--Females				
Anterior pituitary cell hypertrophy	0	0	0	16*
Thyroid,				
Follicular cell hyperplasia	0	0	2	24*
hypertrophy	0	0	1	23*
Reduced colloid	0	0	2	5*

[a]Data were extracted from Study No. 252360, pp. 552, 554, and 557-652.

*Significantly different from control ($p \leq 0.05$)

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

Parameter	Dosage Level (ppm)			
	0	2.5	25	125
No. matings (F_0 parents)	25	25	25	25
Mating index (%)[b]	100	100	100	100
No. pregnancies	24	25	25	24
Fertility index (%)[c]	96.0	100	100	96.0
Gestation index (%)[d]	100	100	100	100
Gestation length (days)	21.5	21.4	21.4	21.7
Total no. stillborn pups[h]	2	0	4	3
Total no. dead pups from Days 1-21[h]	18	16	19	37
Total no. missing pups from Days 1-21[h]	23	17	39	36
Total no. live pups[i]				
Day 1[h]	318	396	354	358
Day 4 precull[h]	301	379	327	318
Day 21	164	187	177	160
Mean no. live pups/litter[i]				
Day 1[h]	13.3	15.8	14.2	14.9
Day 4 precull[h]	12.5	15.2	13.1	13.3
Day 21	6.8	7.5	7.1	6.7
Live birth index (%)[e,h]	99.4	100	98.9	99.2
Viability index (%)[f,h]	94.7	95.7	92.4	88.8
Lactation index (%)[g,h]	90.1	93.5	88.5	86.5
Mean pup body weight (g)				
Day 1	6.1	6.0	6.1	6.1
Day 7	12.2	12.0	12.6	12.3
Day 21	49.4	48.6	49.5	47.9
Sex ratio (% males, day 1)	52	46	51	55

[a]Data were extracted from Study No. 252360, pp. 191-192, 198, 313-320, and 370-429.

[b]Mating index: No. of sperm-positive females/No. of females paired

[c]Fertility index: No. of pregnant females/No. of females mated

[d]Gestation index: No. of dams with live pups at birth/No. of pregnant dams

[e]Live birth index: (No. of pups born alive/No. of pups born) X 100

[f]Viability index: (No. of pups alive on day 4 precull/No. of pups born alive) X 100

[g]Lactation index: (No. of pups alive on day 21/No. of pups born alive on day 4 postcull) X 100

[h]Calculated (but not statistically analyzed) by the reviewers using individual litter data

[i]Excludes pups that were missing

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

Parameter	Dose Level (ppm) 0	2.5	25	125
No. matings (F_1 parents)	25	24	25	24
Mating index-female (%)[b]	100	96.0	100	100
No. pregnancies	20	20	23	22
Fertility index-female (%)[c]	80.0	80.0	92.0	91.7
Gestation index (%)[d]	100.0	100.0	95.7	100.0
Gestation length (days)	21.8	21.8	21.8	22.0
Total no. stillborn pups[h]	3	2	3	1
Total no. dead pups from Days 1-21[h]	52	22	36	30
Total no. missing pups from Days 1-21[h]	47	53	54	51
Total no. live pups[i]				
Day 1[h]	242	237	263	265
Day 4 precull[h]	199	205	235	233
Day 21	106	110	124	121
Mean no. live pups/litter[i]				
Day 1[h]	12.1	11.9	12.0[j]	12.0
Day 4 precull[h]	10.0	10.3	10.7[j]	10.6
Day 21	5.3	5.5	5.6[j]	5.5
Live birth index (%)[e,h]	98.8	99.2	90.1	95.3
Viability index (%)[f,h]	82.2	86.5	89.4	87.9
Lactation index (%)[g,h]	71.1	76.9	77.5	76.6
Mean pup body weight (g)				
Day 1	6.4	6.6	6.3	6.4
Day 7	11.6	11.3	12.2	11.5
Day 21	43.9	44.8	46.0	43.3
Sex ratio (% males, day 1)	44	48	46	48

[a]Data were extracted from Study No. 252360, pp. 194-195, 204, 321-328, and 430-473.

[b]Mating index: No. of sperm-positive females/No. of females paired

[c]Fertility index: No. of pregnant females/No. of females mated

[d]Gestation index: No. of dams with live pups at birth/No. of pregnant dams

[e]Live birth index: (No. of pups born alive/No. of pups born) X 100

[f]Viability index: (No. of pups alive on day 4 precull/No. of pups born alive) X 100

[g]Lactation index: (No. of pups alive on day 21/No. of pups born alive on day 4 postcull) X 100

[h]Calculated (but not statistically analyzed) by the reviewers using individual litter data

[i]Excludes pups that were missing

[j]Sample size N=22; one dam was found dead on GD 19.

APPENDIX

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