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

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7/11/91

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Review of Simazine 2-generation reproduction study in rats.

Tox.Chem No.: 740
HED Project No.: 1-0862
MRID No.: 418036-01

To: Connie Childress PM Team#50
Secial Review and Reregistration Division (H7504C)

From: Henry Spencer, Ph.D. 7/8/91
Acting Section Head
Review Section III
Toxicology Branch I
Health Effects Division (H7509C)

Thru: Karl Baetcke, Ph.D. 7/11/91
Branch Chief
Toxicology Branch I
Health Effects Division (H7509C)

ACTION:

Review Simazine multi-generation reproduction study in rats submitted by the registrant, CIBA-Geigy Corp.

CONCLUSION:

1. The study No. 882095 conducted by CIBA-Geigy Corp., Summit, N.J. and submitted (MRID No. 418036-01) fulfills the requirement for FIFRA registration under 83-4.

2. The study is classified as core minimum.

3. The NOEL for parental toxicity is 10 ppm (0.7 mg/kg) in females. The LEL is 100 ppm (7.04 mg/kg) in females based on decreased body weight and weight gain.

4. Reproductive toxicity was not observed in the study at 500 ppm(HDT).

5. The study review and report should be added to the data base for Simazine.

12-22

EPA: 68D80056
DYNAMAC No.: 372-A
TASK No.: 3-72A
June 13, 1991

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DATA EVALUATION RECORD

SIMAZINE

Two-Generation Reproductive Toxicology Study in Rats

STUDY IDENTIFICATION: Epstein, D.L., Hazelette, J.R., and Yau, E.T. Simazine technical: Two-generation reproductive toxicology study in rats. (Unpublished study No. 882095 conducted by Ciba-Geigy Corporation, Pharmaceuticals Division, Summit, NJ, and submitted by Ciba-Geigy Corporation, Agricultural Division, Greensboro, NC; dated February 12, 1991.) MRID No. 418036-01.

APPROVED BY:

Robert J. Weir, Ph.D.
Program Manager
Dynamac Corporation

Signature:

Date: 6/12/91

1. CHEMICAL: 2-chloro-4,6-bis(ethylamino)-s-triazine.

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2. TEST MATERIAL: Simazine technical, 96.9% pure; white powder; lot No. FL 850614.

3. STUDY/ACTION TYPE: Two-generation reproduction study in rats.

4. STUDY IDENTIFICATION: Epstein, D.L., Hazelette, J.R., and Yau, E.T. Simazine technical: Two-generation reproductive toxicology study in rats. (Unpublished study No. 882095 conducted by Ciba-Geigy Corporation, Pharmaceuticals Division, Summit, NJ, and submitted by Ciba-Geigy Corporation, Agricultural Division, Greensboro, NC; dated February 12, 1991.) MRID No. 418036-01.

5. REVIEWED BY:

Pia Lindström, DPH
Principal Reviewer
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Signature: Pia Lindström
Date: 6/11/91

James R. Plautz, M.S.
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Signature: William L McLellan for
Date: June 13, 1991

6. APPROVED BY:

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Karl Baetcke, Ph.D.
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Date: 7/11/91

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DATA EVALUATION RECORD

STUDY TYPE: Reproductive Toxicity. Guideline § 83-4.

MRID NUMBER: 418036-01.

TEST MATERIAL: Simazine technical, 96.9% pure; white powder; lot No. FL 850614.

SYNONYMS: Cekusan, Cequisa S.A.

STUDY NUMBER: 882095.

SPONSOR: Ciba-Geigy Corporation, Agricultural Division, Greensboro, NC.

TESTING FACILITY: Ciba-Geigy Corporation, Pharmaceuticals Division, Summit, NJ.

TITLE OF REPORT: Simazine Technical: Two-Generation Reproductive Toxicology Study in Rats.

AUTHORS: Epstein, D.L., Hazelette, J.R., and Yau, E.T.

REPORT ISSUED: February 12, 1991.

CONCLUSIONS:

In a two-generation reproduction study, Sprague-Dawley rats were fed diets containing simazine technical at 0, 10, 100, or 500 ppm (during the premating period, for males approximately 0, 0.56, 5.61, and 28.89 mg/kg/day; for females approximately 0, 0.70, 7.04, and 34.96 mg/kg/day). Parental toxicity was observed at 500 ppm as decreased food consumption, body weight, and weight gain, and at 100 ppm as decreased body weight and weight gain. Based on these results, the NOEL and LOEL for parental toxicity were 10 and 100 ppm, respectively.

Reproductive toxicity was not observed at any dose level in any generation. Therefore, the NOEL for reproductive toxicity was 500 ppm; the LOEL was not determined.

Classification: CORE Minimum Data. This study meets the minimum requirements set forth under Guideline § 83-4 for a two-generation reproductive toxicity study in rats. If a protocol is submitted, it may be upgraded to a Guideline study.

A. MATERIALS:

Test Compound:	Purity:	96.9%.
	Description:	White powder.
	Lot No.:	FL 850614.
	Contaminants:	Not reported.
Vehicle:	None used; the test material was administered in the diet.	
Test Animals:	Species:	Rat.
	Strain:	Sprague-Dawley (Crl:COBS CD SD BR).
	Source:	Charles River Breeding Laboratories, Kingston, NY.
	Age:	Males: 39 days, females: 38 days upon receipt.
	Weight:	F_0 males--181-300 g and F_0 females--155-217 g upon receipt.

B. STUDY DESIGN:

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

Mating: After 10 and 13 weeks, respectively, of dietary treatment the F_0 and F_1 parental animals were mated. F_1 parental animals were allowed a 3-week rest period before a second mating. Sibling matings were avoided.

Group Arrangement: F_0 animals were randomly allocated to groups via a computerized randomization table, and F_1 parental animals were allocated (method not specified) to groups as follows:

Test Group	Dietary Concentration (ppm)	Number Assigned per Group F_0 Males	F_0 Females	F_1 Males	F_1 Females
Control	0	30	30	30	30
Low dose	10	30	30	30	30
Mid dose	100	30	30	30	30
High dose	500	30	30	30	30

Dosing: The test material was administered continuously in the diet for two consecutive generations. The test diets (mixtures of test material and Purina Rodent Chow #5002) were stored at room temperature. Frequency of test diet preparation was not reported. Homogeneity of the test material in the diet was determined prior to use and during the study by analyzing mixtures for weeks 1 and 14. Stability of the test material in the diet was assessed prior to study initiation. Concentration analyses of the test material in the diet were conducted on samples from each dose level prior to use for weeks 1, 5, 9, 14, 17, 25, 33, 41, and 52. No rationale was reported for the selection of doses.

Observations: Animals were observed for mortality twice a day and for moribundity and overt signs of toxicity once a day. A more detailed clinical examination was performed weekly at the time of weighing. Body weights of males and nonpregnant females were recorded weekly throughout the study, and body weights of pregnant females were recorded weekly during the premating period, on gestational days (GD) 0, 7, 14, and 20, and on lactational days 0, 7, 14, and 21. Food consumption was recorded weekly throughout the study (except during mating) for males and weekly during the premating period and on GD 0, 7, 14, and 20 for females.

The following data were recorded for each litter:

- Number of stillborn pups on lactational day 0;
- Individual body weight, sex, number of live pups, and clinical observations on lactational days 0, 4, 7, 14, and 21; and

- Cageside observations for mortality and changes in behavior twice daily.

Pups found dead and pups culled on day 4 were given a gross examination for abnormalities in the thoracic and abdominal cavities. Following weaning, 30 male and 30 female F_1 pups per litter were randomly selected as F_1 parental animals. All remaining F_1 pups were given a brief gross examination of the thoracic and abdominal cavities. Five F_{2A} pups/sex/dose group were selected for a complete necropsy and histopathological examination. The remaining F_{2A} pups were evaluated in the same way as the F_1 pups. The F_{2B} male pups were sacrificed on day 4; no gross examination was performed. The F_{2B} female pups were assigned to subsequent studies with the test compound.

Following selection of the F_1 parental animals, the F_0 males and females were sacrificed (by CO_2 inhalation, cervical dislocation, or T-61 ingestion or injection) and subjected to a detailed gross examination (including the number of implantation sites for females). Evaluation of F_1 parental animals was similar to that of F_0 parental animals, with the exception that implantation sites in females were not counted. Parental animals sacrificed prior to schedule or found dead were given a detailed gross examination. The following tissues from parental animals and five randomly selected F_{2A} weanlings/sex/dose group were placed in fixative for processing and histopathological examination:

- Seminal vesicles
- Prostate
- Coagulating gland
- Uterus
- Ovaries*
- Gross lesions
- Testes*
- Epididymides
- Cervix
- Vagina
- Pituitary

For tissues with an asterisk (*), organ weight was recorded. Histopathological evaluations were carried out on tissues from the control and high-dose groups only.

Statistical Analysis: The following analyses were conducted:

- Parental and pup body weights, organ weights, postnatal parameters, and pathology parameters--Bartlett's test for homogeneity, ANOVA, and Dunnett's test (or procedures for unequal variances). The level of significance was $p \leq 0.05$.

Compliance:

- A signed Statement of No Data Confidentiality Claim, dated February 18, 1991, was provided;

- A signed Statement of Compliance with FDA and EPA GLPs, dated February 22, 1991, was provided; and
- A signed Quality Assurance Statement, dated February 11, 1991, was provided.

C. RESULTS:

The following results were reported by the study authors:

1. Test Material Analysis: Concentrations of the test material in the diets ranged from 90 to 111% of the nominal values. Homogeneity analyses revealed concentrations of 97-101% of nominal values. Analyses for stability of the test material in the diet after 41 days at room temperature revealed concentrations of 91-107% of nominal values.

2. Parental Toxicity:

Mortality: No compound-related mortality was observed.

In the F_0 generation at 500 ppm, one male was found dead during the premating phase; necropsy revealed severe pyelonephritis and subacute purulent inflammation in the seminal vesicles. At the same dose level, one female was found dead during the postmating period; necropsy revealed no abnormalities.

In the first mating of the F_1 generation, one male in the control group was found dead during the mating phase; necropsy revealed enlarged kidneys and severe pyelonephritis. At 500 ppm, one male and one female were sacrificed moribund during the mating and postmating phase, respectively; necropsy revealed chronic inflammation of the skin and exostosis in the male, but no abnormalities were noted in the female. Also at 500 ppm, one female was found dead during the postmating phase; necropsy revealed bacteria in the pituitary.

In the second mating of the F_1 generation, one female at 10 ppm and one female at 100 ppm were sacrificed moribund during the mating and postmating phase, respectively; necropsy revealed chronic inflammation of the skin in both animals.

Clinical Observations: No compound-related clinical signs were observed. Frequent observations occurring in all dose groups, including the control group, were alopecia, scab/sore, and chromodacryorrhea.

Body Weight: Summaries of body weights from selected time intervals are presented in Tables 1, 2, and 3. Detailed results are presented in the text.

In the F_0 generation, male body weight was significantly decreased (approximately 10%) at 500 ppm starting on day 14 during the premating phase (Table 1) and remained significantly decreased through the postmating phase (data not shown). Body weight gain (data not shown) for males was significantly decreased on days 0-42, 56-63, 0-70, and 0-105 at 500 ppm (approximately 27%) and on days 0-7, 14-28, and 0-70 at 100 ppm (approximately 13%). Female body weight was significantly decreased at 500 ppm (approximately 10%) starting on day 7 during the premating phase (Table 1) and remained significantly decreased through the gestational (Table 2) and lactational (Table 3) periods, and at 100 ppm (approximately 6%) on premating days 14-28 and 63. Body weight gain (data not shown) for females was significantly decreased on days 0-21 and 28-35 at 500 ppm; it was significantly increased on lactational days 0-21.

In the first mating of the F_1 generation, male body weight was significantly decreased (approximately 13-15%) at 500 ppm starting on day 0 during the premating phase (Table 1) and remained significantly decreased through the postmating phase (data not shown); it was significantly increased at 10 ppm starting on day 49 during the premating phase and remained significantly increased through the postmating phase. Body weight gain (data not shown) for males was significantly decreased on days 0-14, 42-49, 63-77, 0-91, and 0-147 at 500 ppm (8-51%) and on days 7-14 at 100 ppm (approximately 11%); it was significantly increased on days 28-56, 0-91, and 0-147 at 10 ppm. Female body weight was significantly decreased at 500 ppm (approximately 14%) starting on day 0 during the premating phase (Table 1) and remained significantly decreased through the gestational period (Table 2), on lactational days 0-14 (Table 3), and at 100 ppm (approximately 6%) on days 35 and 42 during the premating phase. Body weight gain (data not shown) for females was significantly decreased on days 0-7 during the premating phase at 500 (32-75%) and 100 ppm (approximately 31%); it was significantly increased at 100 ppm on days 7-14 and 42-49 during the premating phase and on days 0-21 at 100 ppm and 14-21 and 0-21 at 500 ppm during the lactational period.

TABLE 1. Summary of Body Weights During the Premating Period for Rats Fed Simazine Technical for Two Successive Generations[a]

Dietary Concentration (ppm)	Mean Body Weight (g ± SD) on Study Day: 0	21	35	56	70
F, Males					
0	261.8 ± 22.1	400.5 ± 31.8	465.8 ± 37.8	535.1 ± 45.9	568.3 ± 54.2
10	271.5 ± 15.6	412.4 ± 35.5	476.5 ± 44.6	551.9 ± 57.2	591.0 ± 64.9
100	265.3 ± 15.5	386.4 ± 22.5	446.4 ± 28.6	511.2 ± 31.7	542.7 ± 34.9
500	272.1 ± 15.3	371.1 ± 20.1*	421.2 ± 27.0*	477.9 ± 33.9*	504.5 ± 38.1*
F, Females					
0	184.3 ± 11.0	240.1 ± 17.2	258.8 ± 20.8	285.4 ± 26.8	300.9 ± 31.4
10	181.5 ± 14.2	238.7 ± 21.1	262.4 ± 25.6	285.5 ± 30.4	302.0 ± 35.4
100	178.8 ± 13.5	224.7 ± 20.0*	245.1 ± 22.1	271.6 ± 29.6	281.6 ± 33.7
500	182.2 ± 12.2	216.9 ± 16.4*	232.0 ± 20.9*	252.6 ± 22.8*	263.2 ± 25.9*
F, Males					
0	214.5 ± 34.0	376.1 ± 37.0	435.9 ± 34.5	498.4 ± 39.2	532.5 ± 45.3
10	222.0 ± 37.3	392.2 ± 38.6	451.6 ± 35.9	527.3 ± 44.0*	567.0 ± 45.9*
100	218.1 ± 18.8	376.7 ± 23.0	439.2 ± 26.3	504.9 ± 32.9	536.7 ± 36.6
500	186.3 ± 26.2*	329.9 ± 29.0*	380.3 ± 32.2*	439.1 ± 37.5*	462.9 ± 38.8*
F, Females					
0	169.1 ± 21.1	244.0 ± 24.0	272.9 ± 23.6	301.9 ± 28.6	321.0 ± 33.4
10	167.1 ± 21.3	242.2 ± 20.9	268.9 ± 20.2	297.4 ± 25.1	317.0 ± 27.7
100	171.6 ± 17.3	239.3 ± 24.0	258.1 ± 26.9*	288.9 ± 31.5	304.9 ± 33.6
500	151.2 ± 15.8*	212.7 ± 19.4*	236.0 ± 22.5*	258.4 ± 25.0*	272.4 ± 25.6*

[a]Data were extracted from study No. 332095, Tables 6.4.1, 6.4.3, 6.12.1, and 6.12.3.

*Significantly different from controls ($p \leq 0.05$).

TABLE 2. Summary of Maternal Body Weights During Gestation in Rats Fed Simazine Technical for Two Successive Generations[a]

Dietary Concentration (ppm)	Mean Body Weight (g ± S.D.) on Gestational Day: 0	7	14	20
F$_0$ generation - F$_1$ litters				
0	302.2 ± 23.2	333.0 ± 26.0	356.4 ± 30.5	419.0 ± 49.2
10	305.4 ± 35.1	339.4 ± 34.1	367.1 ± 33.6	433.6 ± 44.5
100	282.9 ± 33.8	316.9 ± 28.4	343.5 ± 30.1	401.2 ± 51.0
500	262.8 ± 25.2*	286.9 ± 27.7*	313.7 ± 27.4*	374.0 ± 42.8*
F$_1$ generation - F$_2$ litters				
0	325.4 ± 31.4	356.1 ± 33.5	379.7 ± 34.1	441.1 ± 36.7
10	320.1 ± 29.2	347.1 ± 32.9	374.2 ± 28.8	437.8 ± 28.5
100	310.9 ± 32.7	340.3 ± 35.0	363.1 ± 35.5	431.1 ± 37.9
500	281.5 ± 27.8*	306.3 ± 26.5*	332.4 ± 28.2*	398.9 ± 33.5*
F$_2$ generation - F$_3$ litters				
0	361.3 ± 32.7	389.8 ± 33.1	413.8 ± 36.0	464.2 ± 46.3
10	367.5 ± 32.0	398.1 ± 36.3	424.8 ± 37.5	489.3 ± 45.6
100	350.8 ± 47.0	379.2 ± 46.0	407.3 ± 46.8	477.1 ± 52.8
500	308.9 ± 33.3*	336.6 ± 33.2*	366.0 ± 36.4*	432.9 ± 43.5

[a]Data were extracted from study No. 882095, Tables 6.4.4, 6.12.4, and 6.19.4.

*Significantly different from controls ($p \leq 0.05$).

TABLE 3. Summary of Maternal Body Weights During Lactation in Rats Fed Simazine Technical for Two Successive Generations[a]

Dietary Concentration (ppm)	Mean Body Weight (g ± S.D.) on Lactational Day: 0	7	14	21
F$_1$ generation - F$_1$ litters				
0	331.1 ± 31.3	340.0 ± 28.2	347.8 ± 24.4	336.9 ± 18.7
10	337.8 ± 42.8	356.8 ± 31.4	364.1 ± 26.8	342.5 ± 20.7
100	318.0 ± 33.6	340.1 ± 28.7	345.3 ± 26.4	329.7 ± 22.5
500	290.0 ± 27.6*	312.9 ± 22.8*	318.9 ± 20.6*	314.2 ± 22.0*
F$_2$ generation - F$_2$ litters				
0	352.2 ± 38.7	347.8 ± 31.1	357.1 ± 37.6	339.5 ± 32.2
10	353.1 ± 25.4	348.4 ± 18.7	364.3 ± 19.2	347.4 ± 18.5
100	341.6 ± 36.4	344.7 ± 30.6	362.9 ± 25.2	344.4 ± 25.9
500	311.7 ± 29.0*	317.1 ± 33.4*	332.5 ± 31.3*	331.2 ± 25.9
F$_3$ generation - F$_3$ litters				
0	384.4 ± 30.6	380.0 ± 32.6	388.1 ± 34.4	375.9 ± 35.7
10	397.8 ± 37.5	397.9 ± 32.3	392.1 ± 42.0	390.4 ± 31.1
100	383.0 ± 51.9	387.3 ± 41.8	377.9 ± 38.0	385.5 ± 32.9
500	341.2 ± 42.1*	356.4 ± 36.7	359.7 ± 40.0	357.7 ± 31.1

[a]Data were extracted from study No. 882095, Tables 6.4.5, 6.12.5, and 6.19.5.

*Significantly different from controls ($p \leq 0.05$).

In the second mating of the F_1 generation, male body weight was significantly decreased (approximately 16%) at 500 ppm starting on day 154 during the rest phase (Table 1) and remained significantly decreased through the mating and postmating phases; it was significantly increased at 10 ppm during the rest, mating, and postmating phases (data not shown). Body weight gain (data not shown) for males was significantly decreased (approximately 26%) on days 154-175 at 500 ppm and significantly increased on days 154 to term at 100 ppm. Female body weight was significantly decreased at 500 ppm starting on day 154 during the premating phase (approximately 14%; data not shown); on gestational days 0, 7, and 14 (approximately 13%; Table 2); and on lactational day 0 (approximately 11%; Table 3). Body weight gain (data not shown) for females was significantly decreased on days 154-168 during the rest phase (approximately 64%), and significantly increased on gestational days 14-21 and lactational days 0-7 and 0-21 at 500 ppm.

Food Consumption: Summaries of food consumption from selected time intervals are presented in Tables 4 and 5. Detailed results are presented in the text.

In the F_0 generation, daily food consumption among males (reported only for the premating period) was significantly decreased during the entire premating phase (Table 4) at 500 ppm (approximately 11%) and on days 14-21 and 56-63 at 100 ppm (approximately 8%). Daily food consumption among females was significantly decreased at 500 ppm during the premating phase (approximately 9%; Table 4) on days 0-7, 14-21, 28-49, and 56-63 and on gestational days 0-7 (Table 5), and on days 56-63 during the premating phase at 100 ppm (approximately 8%). The daily mean test material intake (data not shown) for the premating phase was 0.60, 6.01, and 29.58 mg/kg for males and 0.72, 7.20, and 36.07 mg/kg for females in the low-, mid- and high-dose groups, respectively.

In the first mating of the F_1 generation, daily food consumption among males was significantly decreased (approximately 12%) during the entire premating phase at 500 ppm (Table 4) and significantly increased on days 35-63 and 77-91 during the premating phase at 10 ppm. Daily food consumption among females was significantly decreased at 500 ppm (approximately 12%) during the entire premating phase (Table 4) and on gestational days 0-7 (Table 5), and on days 21-28 during the premating phase at 100 ppm (approximately 11%) and increased on gestational days 14 to 20 at 10 ppm (Table 5). The daily mean test material intake (data not shown) for the premating phase was 0.69,

TABLE 4. Food Consumption for Selected Weeks During the Premating Period for Rats Fed Simazine Technical for Two Successive Generations[a]

Dietary Concentration (ppm)	Mean Food Consumption (g/animal/day ± SD) for Study Days: 0-7	14-21	35-42	49-56	63-70
F, Males					
0	24.7 ± 2.6	26.9 ± 3.0	26.0 ± 2.2	26.6 ± 2.5	26.8 ± 3.5
10	26.1 ± 2.7	26.9 ± 3.8	26.0 ± 2.7	27.1 ± 3.4	27.3 ± 4.0
100	24.3 ± 1.4	24.7 ± 2.4*	24.8 ± 1.9	25.0 ± 2.3	26.3 ± 1.9
500	22.3 ± 1.6*	23.0 ± 1.5*	22.8 ± 3.5*	24.1 ± 2.3*	24.3 ± 2.3*
F, Females					
0	16.9 ± 2.1	17.6 ± 1.6	17.5 ± 1.9	17.5 ± 2.3	18.1 ± 2.0
10	17.1 ± 1.5	18.4 ± 2.3	17.5 ± 1.9	17.8 ± 2.1	18.5 ± 2.4
100	16.7 ± 2.3	16.7 ± 2.1	16.9 ± 1.9	17.1 ± 2.6	17.7 ± 2.6
500	15.2 ± 1.4*	15.8 ± 1.3*	16.0 ± 1.6*	16.4 ± 1.5	17.3 ± 2.0
F, Males					
0	25.9 ± 2.8	27.3 ± 2.5	26.8 ± 2.6	26.2 ± 1.9	26.4 ± 2.5
10	25.3 ± 2.7	28.1 ± 2.4	29.1 ± 2.8*	28.7 ± 3.0*	27.7 ± 2.6
100	24.3 ± 1.5	26.6 ± 1.9	26.6 ± 1.7	25.9 ± 2.2	25.5 ± 2.1
500	22.1 ± 2.2*	24.1 ± 2.5*	24.1 ± 2.9*	22.9 ± 2.0*	22.2 ± 2.0*
F, Females					
0	18.5 ± 1.7	19.2 ± 2.3	20.4 ± 2.2	19.2 ± 2.6	18.9 ± 2.3
10	17.7 ± 1.7	18.6 ± 1.9	19.2 ± 2.3	19.6 ± 2.1	19.4 ± 2.4
100	17.9 ± 1.8	18.8 ± 2.1	19.6 ± 2.8	19.1 ± 2.1	18.5 ± 2.3
500	16.7 ± 1.4*	17.0 ± 1.5*	17.1 ± 1.5*	16.7 ± 1.5*	16.7 ± 1.6*

[a]Data were extracted from study No. 852095, Tables 6.2.1, 6.2.2, 6.10.1, and 6.10.2.

*Significantly different from Controls ($p \leq 0.05$).

TABLE 5. Summary of Maternal Food Consumption During Gestation in Rats Fed Simazine Technical for Two Successive Generations[a]

Dietary Concentration (ppm)	Mean Food Consumption (g/animal/day ± S.D.) on Gestational Days: 0 - 7	7 - 14	14 - 21
F_0 generation - F_1 litters			
0	21.3 ± 2.0	22.3 ± 2.4	22.3 ± 4.0
10	22.2 ± 3.4	23.5 ± 2.2	21.7 ± 4.9
100	21.9 ± 2.9	22.2 ± 3.5	21.0 ± 6.1
500	19.2 ± 3.4*	21.6 ± 2.0	21.0 ± 5.9
F_1 generation - F_2 litters			
0	20.9 ± 3.0	22.3 ± 2.4	21.8 ± 2.7
10	22.4 ± 2.1	23.9 ± 2.4*	23.7 ± 1.8*
100	21.0 ± 2.4	22.2 ± 2.3	22.3 ± 2.9
500	18.7 ± 1.9*	20.9 ± 2.0	22.0 ± 1.7
F_2 generation - F_3 litters			
0	25.1 ± 2.8	26.0 ± 2.5	24.0 ± 3.1
10	26.1 ± 2.7	26.7 ± 2.5	25.9 ± 2.8
100	24.2 ± 2.7	25.1 ± 2.8	25.4 ± 2.9
500	21.7 ± 2.2*	23.6 ± 2.4*	25.6 ± 4.1

[a]Data were extracted from study No. 882095, Tables 6.2.3, 6.10.3, and 6.17.3.

*Significantly different from controls ($p \leq 0.05$).

6.70, and 34.83 mg/kg for males and 0.77, 7.64, and 38.79 mg/kg for females in the low-, mid-, and high-dose groups, respectively.

In the second mating of the F_1 generation, daily food consumption was significantly decreased among males (approximately 10%) and females (approximately 18%) during the entire rest period (data not shown) and among females on gestational days 0-14 (Table 5) at 500 ppm. The daily mean test material intake (data not shown) for the rest period was 0.40, 4.13, and 22.27 mg/kg for males and 0.61, 6.29, and 30.01 mg/kg for females in the low-, mid- and high-dose groups, respectively.

Gross and Microscopic Pathology: No gross compound-related findings were observed in any generation at any dose level.

A summary of parental reproductive organ weights is presented in Table 6. In the F_0 generation, relative (to body weight) testicular weight was significantly increased at 500 ppm. In the F_1 generation, relative testicular and ovarian weights were significantly increased at 500 ppm. Microscopic examination of tissues from animals in both generations revealed no compound-related differences between the control and treated groups.

3. Reproductive Toxicity: The effects of dietary administration of the test material on reproductive parameters are summarized in Tables 7, 8, and 9. No compound-related effects were observed in any generation at any dose level. In the F_1 offspring, male pup body weights were significantly increased on days 14 and 21 at 10 ppm; in the F_2 offspring, male pup body weights were significantly increased on day 14 at 100 ppm. Incidental clinical observations and gross malformations in pups were observed in both generations in all dose groups, including the control groups.

C. REVIEWERS' DISCUSSION/CONCLUSIONS:

1. Test Material Analyses: Homogeneity and stability (for 41 days at room temperature) of the test compound in the diet were confirmed. Throughout the study, concentrations of the test compound in the diet were within ±15% of nominal concentrations.

2. Parental Toxicity: Compound-related parental toxicity was observed at 500 and 100 ppm. At 500 ppm, significant decreases were consistently present in food consumption, body weight, and body weight gain. The relative increases in testicular and ovarian weights were considered to be

TABLE 6. Ovary and Testes Weights for Rats Fed Simazine Technical for Two Successive Generations[a]

Organ	Dietary Concentration (ppm) 0	10	100	500
TESTES				
F_0 generation:				
Absolute (g)	3.53 ± 0.23	3.51 ± 0.64	3.53 ± 0.44	3.56 ± 0.33
Relative (to BW, %)	0.61 ± 0.07	0.58 ± 0.11	0.63 ± 0.08	0.68 ± 0.08*
F_1 generation, 2nd mating:				
Absolute (g)	3.80 ± 0.32	3.98 ± 0.39	3.82 ± 0.24	3.92 . 0.39
Relative (to BW, %)	0.59 ± 0.07	0.58 ± 0.08	0.57 ± 0.05	0.71 ± 0.09*
OVARIES				
F_0 generation:				
Absolute (g)	0.10 ± 0.02	0.10 ± 0.02	0.10 ± 0.03	0.10 ± 0.02
Relative (to BW, %)	0.03 ± 0.01	0.03 ± 0.01	0.03 ± 0.01	0.04 ± 0.01
F_1 generation, 2nd mating:				
Absolute (g)	0.08 ± 0.03	0.08 ± 0.03	0.08 ± 0.03	0.08 ± 0.03
Relative (to BW, %)	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.03 ± 0.01*

[a]Date were extracted from Study No. 882095, Tables 6.7.1, 6.7.2, 6.22.1, and 6.22.2.

*Significantly different from controls ($p \leq 0.05$).

TABLE 7. Summary of Effects of Dietary Administration of Simazine Technical on F_1 Reproductive Parameters, Offspring Survival, and Pup Body Weight[a]

Parameter	Dietary Concentration (ppm) 0	10	100	500
No. matings	30	28	30	29
No. pregnancies	24	25	27	28
Fertility index-female (%)	80	89	90	97
Gestation index (%)	100	100	100	100
Gestation length (days)	23.3	23.3	23.4	23.3
Implantation sites/litter	14.9	16.0	15.0	14.8
Total No. live pups[b]				
Day 0	319	339	333	378
Day 4 (precull)	315	332	317	354
Day 21	182	186	191	211
Mean No. live pups/litter				
Day 0	13.3	13.6	12.3	13.5
Day 4 (precull)	13.1	13.3	11.7	12.6
Day 21	7.6	7.4	7.1	7.5
Live birth index (%)[b,c,d]	99 (24)	93 (25)	93 (27)	98 (28)
Viability index (%)[e]	99	95	93	96
Lactation index (%)[f]	99	99	96	99
Mean pup body weight/litter (g)				
Day 0, male	6.5	6.4	6.6	6.4
female	6.1	6.1	6.1	6.2
Day 4, male (precull)	9.5	9.9	9.9	9.5
female (precull)	9.1	9.4	9.5	9.2
Day 14, male	30.8	33.0*	32.2	30.8
female	30.3	31.3	31.1	29.9
Day 21, male	51.1	54.8*	54.2	49.4
female	50.1	52.0	52.0	47.7
Sex ratio (% male)	53	49	52	46

[a]Data were extracted from study No. 882095, Tables 6.6.2-6.6.4, 6.8.1, and 6.8.3.

[b]Calculated by the reviewers.

[c]Number of litters within parenthesis.

[d]Live birth index was calculated as: $\frac{\text{No. of live pups born}}{\text{No. of live and dead pups born}} \times 100.$

[e]Viability index was calculated as: $\frac{\text{No. of pups alive on Day 4 precull}}{\text{No. of pups alive on day 0}} \times 100.$

[f]Lactation index was calculated as: $\frac{\text{No. of pups alive on Day 21}}{\text{No. of pups alive on Day 4 postcull}} \times 100.$

*Significantly different from controls ($p \leq 0.05$).

TABLE 8. Summary of Effects of Dietary Administration of Simazine Technical on F_{2A} Reproductive Parameters, Offspring Survival, and Pup Body Weight[a]

Parameter	Dietary Concentration (ppm) 0	10	100	500
No. matings	23	27	27	30
No. pregnancies	20	22	22	28
Fertility index-female (%)	77	90	90	100
Gestation index (%)	100	96	100	96
Gestation length (days)	23.6	23.1	23.2	23.2
Total No. live pups[b]				
Day 0	262	268	291	343
Day 4 (precull)	254	264	283	337
Day 21	151	144	174	196
Mean No. live pups/litter				
Day 0	13.1	13.4	13.2	12.7
Day 4 (precull)	12.7	13.2	12.9	12.5
Day 21	7.6	7.2	7.9	7.3
Live birth index (%)[b,c,e]	98 (20)	98 (20)	96 (22)	95 (27)
Viability index (%)[e]	97	99	98	95
Lactation index (%)[f]	100	94	99	96
Mean pup body weight/litter (g)				
Day 0, male	6.4	6.2	6.4	6.5
female	6.0	5.9	6.0	6.2
Day 4, male (precull)	9.4	8.8	9.5	9.6
female (precull)	9.1	8.4	9.0	9.0
Day 14, male	28.9	29.2	30.7	29.4
female	28.6	27.0	29.4	28.1
Day 21, male	48.1	48.1	49.7	46.3
female	46.3	44.2	47.5	43.9
Sex ratio (% male)	55	50	53	51

[a]Data were extracted from study No. 882095, Tables 6.14.2-6.14.4, 6.15.1, and 6.15.3.

[b]Calculated by the reviewers.

[c]Number of litters within parenthesis.

[d]Live birth index was calculated as: $\frac{\text{No. of live pups born}}{\text{No. of live and dead pups born}} \times 100.$

[e]Viability index was calculated as: $\frac{\text{No. of pups alive on Day 4 precull}}{\text{No. of pups alive on Day 0}} \times 100.$

[f]Lactation index was calculated as: $\frac{\text{No. of pups alive on Day 21}}{\text{No. of pups alive on Day 4 postcull}} \times 100.$

[g]Significantly different from controls ($p \leq 0.05$).

TABLE 9. Summary of Effects of Dietary Administration of Simazine Technical on F_{2a} Reproductive Parameters, Offspring Survival, and Pup Body Weight[a]

Parameter	Dietary Concentration (ppm)			
	0	10	100	500
No. matings	23	26	29	28
No. pregnancies	12	17	17	19
Fertility index-female (%)	52	65	59	68
Gestation index (%)	100	100	100	100
Gestation length (days)	23.7	23.4	23.5	23.3
Total No. live pups[b] Day 0	129	212	207	197
Mean No. live pups/litter Day 0	10.8	12.5	12.9	10.9
Live birth index (%)[b,c,d]	98 (12)	97 (17)	98 (16)	90 (18)
Sex ratio (% male)	51	50	52	44

[a]Data were extracted from study No. 882095, Tables 6.21.2-6.21.4 and 6.23.1.

[b]Calculated by the reviewers.

[c]Number of litters within parenthesis.

[d]Live birth index was calculated as: $\frac{\text{No. of live pups born}}{\text{No. of live and dead pups born}} \times 100.$

secondary effects because of the weight loss that the animals experienced at this dose level and were therefore not an effect of the test material. At 100 ppm, a consistent, but not always significant, decrease was observed in body weight. Because this decrease was present in both sexes and generations, and because decreased body weight occurred in a dose-related manner, the effects at 100 ppm were considered to be compound related. The sporadically decreased food consumption that was noted at 100 ppm was not considered to be an effect of the test compound.

Based on the decreased body weight, the parental toxicity NOEL and LOEL were 10 and 100 ppm, respectively.

3. Reproductive Toxicity: No compound-related effects were observed in this study. The mean numbers of stillborn pups per litter (Table 10) were slightly but nonsignificantly increased for the F_1 pups at 10 and 100 ppm and for F_{2A} and F_{2B} pups at 500 ppm. In each of these groups, an increased number of dead pups (9-16) in one single litter was responsible for this increase. The reviewers did not consider these increases to be compound-related effects but rather normal variations since they occurred in only one litter in the respective dose groups; they did not occur in a dose-related manner; and no consistent pattern was noted across the two generations. This conclusion is further supported by the fact that no changes were noted in the numbers of viable neonates per litter and in the live birth indices.

The sex ratio (% male) was slightly decreased at 500 ppm for F_1 pups (Table 7; 46%) and F_{2B} pups (Table 9; 44%). The reviewers did not consider these decreases to be compound-related effects because they were not significant; they did not occur among F_{2A} pups; and when survival indices to day 21 were reported separately for males and females (data not shown), no differences were noted between the sexes, the dose groups and the generations.

Based on these results, the NOEL for reproductive toxicity was 500 ppm; the LOEL was not determined.

4. Study (Reporting) Deficiencies:

No protocol was submitted.

TABLE 10. Number of Stillborn Pups in Rats Fed Simazine Technical for Two Successive Generations[a]

	Dietary Concentration (ppm)			
	0	10	100	500
F_0 generation/F_1 pups				
No. of viable litters	24	25	27	28
Total No. stillbirths/No. pups (%)	5/324 (1.5)	24/363 (6.6)	26/359 (7.2)	7/385 (1.8)
No. stillbirths/litter (%)	0.21 ± 0.66[b] (1.6)	0.96 ± 2.82 (7.4)	0.96 ± 2.01 (7.2)	0.25 ± 0.52 (3.6)
No. of viable neonates/litter	13.29 ± 3.78	13.56 ± 4.09	12.33 ± 4.16	13.50 ± 3.79
F_1 generation/F_{2A} pups				
No. of viable litters	20	20	22	27
Total No. stillbirths/No. pups (%)	4/266 (1.5)	5/273 (1.8)	12/303 (4.0)	19/362 (5.3)
No. stillbirths/litter (%)	0.20 ± 0.52 (3.3)	0.25 ± 0.55[c] (3.3)	0.59 ± 1.01 (4.4)	0.70 ± 2.49 (5.1)
No. of viable neonates/litter	13.10 ± 3.93	13.40 ± 3.57[c]	13.23 ± 3.24	12.70 ± 3.97
F_1 generation/F_{2B} pups				
No. of viable litters	12	17	17	19
Total No. stillbirths/No. pups (%)	3/132 (2.3)	7/219 (3.2)	4/211 (1.9)	21/218 (9.6)
No. stillbirths/litter (%)	0.25 ± 0.62 (5.3)	0.41 ± 0.80 (2.8)	0.25 ± 0.77[d] (3.5)	1.17 ± 3.75[d] (7.0)
No. of viable neonates/litter	10.75 ± 6.12	12.47 ± 3.66	12.94 ± 4.81[d]	10.94 ± 5.01[d]

[a]Data were extracted from Study No. 882095, Tables 6.6, 6.8, 6.14-15, 6.21, and 6.23, and from individual animal data.

[b]Mean ± S.D.

[c]Two litters were excluded from the calculation as day 0 lactation was unknown.

[d]One litter was excluded from the calculation as day 0 lactation was unknown.

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D. CLASSIFICATION: CORE Minimum Data.

Parental Toxicity NOEL = 10 ppm.
(approximately 0.63 mg/kg/day)

Parental Toxicity LOEL = 100 ppm.
(approximately 6.33 mg/kg/day)

Reproductive Toxicity NOEL = 500 ppm.
(approximately 31.93 mg/kg/day)

Reproductive Toxicity LOEL = Not determined.

E. RISK ASSESSMENT: Not Applicable.