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DATA EVALUATION RECORD

STUDY TYPE: Reproduction and Fertility Effects Study - [rat] OPPTS 870.3800 [§83-4]; OECD 416.

PC CODE: 014019

DP BARCODE: D279817
SUBMISSION NO.: S604757

TEST MATERIAL (PURITY): YRC 2894 (Thiacloprid; 96.7-97.5% a.i.)

SYNONYMS: (3-[(6-chloro-3-pyridinyl)methyl]-2-thiazolidinylidene]-cyanamide

CITATION: Eigenberg, D.A. (1997) A two-generation dietary reproduction study in rats using technical YRC 2894. Bayer Corporation, Agricultural Division Toxicology, Stilwell, KS. Laboratory Study No.: 95-672-FV. December 8, 1997. MRID 44927702. Unpublished.

Porter, M.C., V. Jasty, D.S. Grosso, et.al. (1995) A two-generation reproduction range-finding study with YRC-2894 technical in rats. Miles Inc. Elkhart, IN. Laboratory Project Id.: MTD9425/PH24084, May 25, 1995. MRID 44927638. Unpublished.

SPONSOR: Bayer Corporation, Agriculture Division, Box 4913, Hawthorn Road, Kansas City, MO

EXECUTIVE SUMMARY: In a two-generation reproduction toxicity study (1995 and 1997, MRIDs 44927702 and 44927638), YRC 2894 (Thiacloprid; 96.7-97.5% a.i.; Lot/batch #290894) was administered to Sprague Dawley rats (30/sex/dose) at nominal dietary dose levels of 0, 50, 300, or 600 ppm (equivalent to 0/0, 3.5/4.2, 21/26, and 41/51 mg/kg bw/day for males/females). The P animals were dosed for approximately 10 weeks prior to mating to produce the F_1 litters. After weaning, F_1 animals (30/sex/dose) were selected to and were dosed for approximately 10 weeks prior to mating to produce the F_2 litters.

Systemic effects. Parental P1 body weights were decreased at 300 ppm on GD 0 and at 600 ppm during the last three weeks of premating and throughout most of gestation and lactation. In the 600 ppm F_1 animals, body weights were decreased in the males throughout the study and in the females throughout premating, gestation, and lactation. In the 300 ppm F_1 males, food consumption was increased during weeks 8 and 10. Food consumption was increased during premating in the F_1 males during weeks 2-12 (except week 11) and in the F_1 females during

weeks 2, 5, and 8-10. Absolute and relative (to body weight) **liver weights** were increased in the 300 ppm males and 600 ppm males and females in the P generation. In the F_1 generation parents, absolute and relative liver weights were increased in the 300 and 600 ppm females. In the F_1 males, relative liver weights were increased at 600 ppm. **Hepatocytomegaly** was increased in incidence and severity (minimal to slight) in the 300 and 600 ppm males and females in the P and F_1 generations. Dose-dependent increases (not significant) in the incidence and severity (minimal to moderate) of necrosis were observed in the liver in the P females. Absolute and relative (to body weight) **thyroid weights** were increased in the 300 ppm females and 600 ppm males and females in the P generation. In the F_1 generation parents, relative thyroid weights were increased in the 300 ppm males and 600 ppm males and females. In both generations, incidences of **thyroid follicular cell hypertrophy** were increased in the 300 ppm females and 600 ppm males and females. Average severity (minimal to slight) of follicular cell hypertrophy was dose-dependently increased in the F_1 generation. **The LOAEL for parental systemic toxicity is 300 ppm (21 mg/kg/day) based on increased liver and thyroid weights and on hepatocyto-megaly, liver necrosis, and thyroid follicular cell hypertrophy. The NOAEL is 50 ppm (3.5 mg/kg/day).**

Reproductive performance. Estrous cycle length and periodicity, reproductive performance (mating index, fertility index, and gestation length), pup clinical signs, sex ratio, implantation sites, birth index, and lactation index were unaffected by treatment. In the P generation, four dams at 300 ppm and three dams at 600 ppm were found dead or sacrificed on GD 23-24 because of **dystocia**. Paleness and stained/wet ventrum were associated with dystocia in these animals. Dystocia was not noted in the F1 parental group. **The LOAEL for reproductive performance is 300 ppm (26 mg/kg/day) based on dystocia. The NOAEL for reproductive performance is 50 ppm (4.2 mg/kg/day).**

Developmental toxicity. At 300 ppm, **pup weights** were decreased after PND 14 in the F_1 females and in the F_2 males and females. Pup weights were decreased in the 600 ppm F_1 and F_2 litters after PND 7; the magnitude of the decrease was more pronounced as lactation proceeded. The number of stillborn pups was increased in all treated F_1 groups (2, 16, 13, and 16 in the 0, 50, 300, and 600 ppm groups, respectively) but there was no dose response. The **live birth index** was decreased (not significant) at 600 ppm in the F_1 and F_2 generations. In the F_1 generation pups, the **viability index** (days 0-4) was decreased (not significant) at 600 ppm. **The LOAEL for offspring toxicity is 300 ppm based on decreased pup weight during lactation. The NOAEL is 50 ppm.**

The study is **acceptable/guideline** and satisfies the requirements for a two-generation reproduction study (OPPTS 870.3800; OECD 416) in the rat.

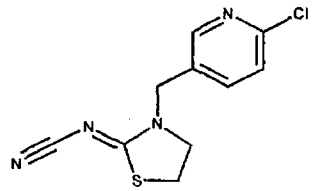
COMPLIANCE: Signed and dated Data Confidentiality, GLP, Flagging, and Quality Assurance statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: YRC 2894

Description:	Pale yellow powder
Lot/Batch #:	290894
Purity:	96.7-97.5% a.i.
Compound Stability:	The test substance was stable in the diet for 7 days frozen followed by 7 days at room temperature.
CAS # of TGAI:	111988-49-9
Structure:	



2. Vehicle: Diet

3. Test animals

Species:	Rat
Strain:	Sprague-Dawley
Age at study initiation:	(P) 7 weeks; (F_1) 21 days
Mean wt. at study initiation:	(P) Males: 217.4-222.6 g; Females: 148.3-151.4 g (F_1) Males: 177.9-216.6 g; Females: 145.1-160.0 g
Source:	Sasco Inc., St. Louis, MO
Housing:	Individually, in suspended stainless steel cages, except during mating Females were housed individually in polycarbonate cages during gestation and lactation.
Diet:	Rodent Laboratory Chow 5001-4, Etts form (Purina), *ad libitum*
Water:	Tap water, *ad libitum*
Environmental conditions:	**Temperature:** 64-78°F **Humidity:** 40-70% **Air changes:** Not reported **Photoperiod:** 12 hrs dark/12 hrs light
Acclimation period:	2 weeks

B. PROCEDURES AND STUDY DESIGN

1. Mating procedure: Breeding was accomplished by co-housing one female with the same male for up to 21 consecutive days. Upon confirmed insemination (presence of a vaginal plug and/or the presence of sperm in a daily vaginal lavage), each female was placed in a plastic nesting cage. The day of confirmed insemination was designated as gestation day (GD) 0. Females which were never observed as being inseminated were placed in nesting cages at the end of the breeding period and treated as if pregnant (in case insemination occurred without being detected).

2. Study schedule: The P and F_1 parental animals were given test diets for approximately 10 weeks before they were mated. Selection of parents for the F_1 generation was made when the pups were weaned at 21 days of age, and the F_1 parental animals were mated approximately 12 weeks after selection.

3. Animal assignment: P animals were randomly assigned (stratified by body weight) to test groups as seen in Table 1.

TABLE 1. Animal assignment

Test Group	Dose in Diet [a] (ppm)	Animals/group			
		P Males	P Females	F_1 Males	F_1 Females
Control	0	30	30	30	30
Low (LDT)	50	30	30	30	30
Mid (MDT)	300	30	30	30	30
High (HDT)	600	30	30	30	30

a Diets were administered continuously throughout the study.

4. Dose selection rationale: The dose levels summarized in Table 1 were chosen based on the results of a two-generation range-finding study (1995, MRID 44927638), included as an Appendix to this DER.

5. Dosage preparation and analysis: Test diets were prepared weekly by dissolving/suspending the appropriate amount of test substance for each dose level in acetone and corn oil. This suspension was then added to the diet so that all test diets were 1% corn oil and had the same quantity of acetone added. Diet batches were stored frozen (-23°C) and thawed prior to presentation to the animals each week. Homogeneity (top, middle, bottom) of the test substance in the diet was analyzed for 20 and 2000 ppm samples. Stability of the test substance in the diet (20 and 2000 ppm) was assessed under freezer conditions for up to 28 days and at room temperature for up to 14 days. Freezer samples were collected for analysis on days 7, 14, 21, and 28; room temperature samples were collected for analysis on days 0, 1, 3, 7, 10, and 14 days following freezer storage for 7 days. Concentration analyses were performed for formulations prepared for study weeks 1, 10, 18, 27, and 36.

Results:

Homogeneity (mean % of nominal)
20 ppm: 97.7%, CV = 5%
2000 ppm: 90.7%, CV = 5%

Stability (range as % day 0)
Room temperature for 7 days after 7 days frozen: 83.2-90.7%
Frozen for 28 days: 93.9-95.9%

Concentration (% of nominal)
50 ppm: 91.7%, CV = 8%
300 ppm: 93.2%, CV = 7%
600 ppm: 90.3%, CV = 7%

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

C. OBSERVATIONS

1. **Parental animals:** All animals were observed twice daily (once daily on weekends and public holidays) for mortality, moribundity, and clinical signs of toxicity. Detailed clinical examinations were performed weekly. For the females, body weights were measured weekly during premating, on GDs 0, 6, 13, and 20, and on LDs 0, 4, 7, 14, and 21. Food consumption was measured weekly during premating and gestation, twice a week during the first week of lactation, and weekly during weeks 2 and 3 of lactation. For the males, body weights were measured weekly throughout the study; food consumption was measured weekly during the premating period and for the two weeks following mating of the F_1 animals. Test substance intake was calculated using the analytical concentration, food consumption, and body weight data. Estrous cycle stage (diestrus, proestrus, or estrus) was determined microscopically from vaginal smears taken for three weeks prior to mating from ten P and ten F_1 females per dose group. Sperm enumeration, motility, and morphology were not evaluated.

2. **Litter observations:** The following litter parameters (X) were observed (Table 2).

TABLE 2. F_1 / F_2 litter observations[a]

Observation	Time of observation (lactation day)					
	Day 0	Day 4 [b]	Day 4 [c]	Day 7	Day 14	Day 21
Number of live pups	X	X	X	X	X	X
Pup weight	X	X	X	X	X	X
External alterations	X	X	X	X	X	X
Number of dead pups	X	X	X	X	X	X
Sex of each pup (M/F)	X	X	X	X	X	X

a Data obtained from page 24 and Appendix XV and XVI on pages 285 through 325 in the study report (MRID 44927702).
b Before standardization (culling)
c After standardization (culling)

Clinical observations of the pups were recorded daily throughout lactation. On day 4 postpartum, litters were standardized to a maximum of 8 pups/litter (4/sex/litter, as nearly as possible); adjustments were made by random selection of male and female pups from each litter. Excess pups were sacrificed and subjected to a gross necropsy.

3. Postmortem observations

1) Parental animals: Parental males were sacrificed after completion of the mating phase. Maternal animals were sacrificed after each dam's pups were weaned or on GD 24 if parturition had not occurred. These animals were subjected to a gross necropsy. The following tissues (X) were prepared for microscopic examination, and additionally, the (XX) organs were weighed:

XX	Ovaries	XX	Testes
X	Uterus	X	Epididymides
X	Vagina	X	Prostate
X	Cervix	X	Seminal vesicles
X	Lesions	X	Coagulating gland
XX	Liver		
XX	Thyroid		
X	Pituitary		

2) Offspring: The F_1 offspring not selected as parental animals and all F_2 offspring were sacrificed on PND 21. These weanlings and all culled pups were subjected to a gross necropsy. Microscopic examinations were not performed.

D. DATA ANALYSIS

1. Statistical analyses: Statistical significance was denoted at $p \leq 0.05$ for all tests except Bartlett's ($p \leq 0.001$). The following statistical tests were applied to the data:

Parameter	Statistical test
Body weight Food consumption	ANOVA followed by Dunnett's test as necessary
Number of estrous cycles Estrous cycle length	Kruskal-Wallis followed by Mann-Whitney U-test as necessary
Time to insemination Length of gestation Litter size Viability index Birth index Live birth index Number of stillborn pups per litter Percent of male pups Number of implantation sites	Kruskal-Wallis followed by Dunn's test as necessary
Clinical signs Number of dams with cannibalized pups Mating index Fertility index Gestation index	Chi-square test followed by Fisher's exact test with Bonferroni adjustment as necessary
Terminal body weights Organ weights	Bartlett's test for homogeneity of variances followed by ANOVA and Dunnett's (as necessary) if variances were homogeneous or by Kruskal-Wallis and Mann-Whitney U-test (as necessary) if variances were heterogeneous
Pup gross pathology lesion frequency Adult histopathology lesion frequency	Chi-square test followed by Fisher's exact test as necessary

2. Indices: The following reproductive/viability indices were calculated from breeding and parturition records of animals in the study:

Mating index (%) = # inseminated females/# females co-housed with males x 100

Fertility index (%) = # pregnant females/# inseminated females x 100

Gestation index (%) = # females with live pups/# pregnant females x 100

Birth index (%) = total # pups born per litter/total # implantation sites per dam x 100

Live birth index (%) = # live pups born per litter/total # pups per litter x 100

Viability index (%) = # live pups per litter on day 4 preculling/# live pups born per litter x

100

Lactation index (%) = # live pups per litter on day 21/
 # live pups per litter on day 4 post-culling x 100

3. Historical control data: Historical control values of stillbirths, live birth indices, and viability indices from ten studies conducted from 1988-1994 were provided in Appendix XVII on pages 326-328 of the study report (MRID 44927702).

II. RESULTS

A. PARENTAL ANIMALS

1. Mortality and clinical signs: In the P generation, four dams at 300 ppm and three dams at 600 ppm were found dead or sacrificed on GD 23-24 and dystocia was determined to be the cause of death. One of the 600 ppm dams suffering with dystocia (#FV3104) was weak and pale.

Aside from the signs of dystocia, there were no treatment-related clinical signs in the P or F_1 generations. Several clinical signs (such as lacrimation, hair loss/thinning, and nasal stain) were noted but were considered unrelated to treatment because they were minimal and/or not dose-related in incidence and/or severity.

2. Body weight and food consumption: In the P animals (Tables 3a and 4a), body weights were decreased (↓5%; $p \leq 0.05$) in the 300 ppm females at GD 0. Body weights of the males were comparable to the controls throughout the study. body weights of the 600 ppm females were decreased ($p \leq 0.05$) during the last three weeks of premating and throughout gestation (except on GD 6) and lactation (↓4-8%). There were no treatment-related effects on food consumption in the P animals. During premating, food consumption was incidentally increased ($p \leq 0.05$) in the 600 ppm males during week 2 (↑5%) and sporadically decreased ($p \leq 0.05$) in a manner unrelated to dose in the 50 and 300 ppm females (↓4-9%).

In the 600 ppm F_1 animals (Tables 3b and 4b), body weights were decreased ($p \leq 0.05$) in the males throughout the study (↓14-19%) and in the females throughout premating (↓8-10%), gestation (↓7-9%), and lactation (↓5-10%). In the 300 ppm males, food consumption was increased (↑5-7%; $p \leq 0.05$) during weeks 8 and 10. Food consumption was increased (↑5-9%; $p \leq 0.05$) during premating in the males at this dose during weeks 2-12 (except week 11) and in the females during weeks 2, 5, and 8-10. Food consumption was comparable to controls throughout gestation and lactation.

No treatment-related differences in body weights or food consumption were noted in the 50 ppm animals.

TABLE 3a. Mean (±SE) body weight and food consumption - premating, P generation [a]

Observations/study day	Dose Group (ppm)			
	Control	50	300	600
P Generation Males - Pre-mating				
Mean body weight (g) Day 0	219.0 ± 3.52	217.4 ± 2.91	221.9 ± 3.36	222.6 ± 3.00
Mean body weight (g) Day 35	345.3 ± 6.76	341.5 ± 5.34	344.9 ± 5.26	339.9 ± 5.06
Mean body weight (g) Day 70	395.4 ± 8.46	395.5 ± 6.78	397.4 ± 6.32	392.2 ± 6.62
Pre-mating body weight gain (g) [b] Days 0-70	176.4	178.1	175.5	169.6
Mean food consumption (g/kg/day) Week 1	114.3 ± 1.49	114.1 ± 1.98	113.3 ± 2.10	108.4 ± 1.73
Mean food consumption (g/kg/day) Week 5	67.1 ± 0.68	70.7 ± 1.09	69.1 ± 0.72	69.3 ± 1.38
Mean food consumption (g/kg/day) Week 10	58.1 ± 0.37	59.8 ± 0.69	58.7 ± 0.61	59.6 ± 0.42
P Generation Females - Pre-mating				
Mean body weight (g) Day 0	148.3 ± 1.67	148.5 ± 1.97	150.6 ± 1.86	151.4 ± 1.80
Mean body weight (g) Day 56	220.2 ± 2.68	222.3 ± 3.43	216.4 ± 2.88	210.7 ± 2.83* (↓4)
Mean body weight (g) Day 70	229.8 ± 2.97	228.0 ± 3.53	220.9 ± 3.20	218.4 ± 2.85* (↓5)
Pre-mating body weight gain (g) [b] Days 0-70	81.5	79.5	70.3	67.0
Mean food consumption (g/kg/day) Week 1	143.6 ± 3.89	136.8 ± 3.79	131.0 ± 3.33	133.3 ± 4.10
Mean food consumption (g/kg/day) Week 5	85.6 ± 1.18	85.5 ± 1.44	85.0 ± 1.24	85.5 ± 1.92
Mean food consumption (g/kg/day) Week 10	75.8 ± 1.11	71.3 ± 0.97** (↓6)	73.0 ± 1.04	75.7 ± 0.85

a Data were obtained from Tables 2 and 3, pages 47, 48, 52, and 53 in the study report (MRID 44927702); n=29-30. Percent difference from controls (calculated by the reviewers) is included in parentheses.
b Calculated by the reviewers from data presented in this table.
* Statistically different from control at $p \leq 0.05$
** Statistically different from control at $p \leq 0.01$

TABLE 3b. Mean (±SE) Body weight and food consumption - premating, F_1 generation [a]

Observations/study day	Dose Group (ppm)			
	Control	50	300	600
F_1 Generation Males - Premating				
Mean body weight (g) Day 0	216.6 ± 5.98	208.0 ± 4.82	213.3 ± 4.25	177.9 ± 4.93** (↓18)
Mean body weight (g) Day 7	265.6 ± 5.45	257.9 ± 4.62	258.2 ± 5.56	216.2 ± 5.01** (↓19)
Mean body weight (g) Day 70	410.1 ± 7.09	393.0 ± 5.49	403.6 ± 7.21	351.3 ± 4.62** (↓14)
Overall body weight gain (g) [b] Days 0-70	193.5	185.0	190.3	173.4
Mean food consumption (g/kg/day) Week 3	86.9 ± 1.34	89.1 ± 1.57	90.8 ± 1.04	94.8 ± 1.62** (↑9)
Mean food consumption (g/kg/day) Week 12	56.2 ± 0.67	56.4 ± 0.71	58.7 ± 1.05	59.3 ± 0.62** (↑6)
F_1 Generation Females - Pre-mating				
Mean body weight (g) Day 0	157.6 ± 2.87	156.1 ± 3.34	160.0 ± 2.53	145.1 ± 2.68** (↓8)
Mean body weight (g) Day 21	203.4 ± 4.06	204.0 ± 3.67	199.1 ± 2.77	184.0 ± 3.03** (↓10)
Mean body weight (g) Day 70	242.3 ± 3.45	249.4 ± 3.37	237.1 ± 2.81	222.2 ± 3.52** (↓8)
Overall body weight gain (g) [b] Days 0-70	84.7	93.3	77.1	77.1
Mean food consumption (g/kg/day) Week 2	105.3 ± 1.43	106.6 ± 2.32	104.1 ± 1.45	110.8 ± 1.73* (↑5)
Mean food consumption (g/kg/day) Week 9	76.8 ± 0.83	76.8 ± 0.99	79.7 ± 1.07	82.6 ± 0.88** (↑8)

a Data obtained from Tables 2 and 3, pages 49, 50, 54 , and 55 in the study report (MRID 44927702); n=29-30. Percent difference from controls (calculated by the reviewers) is included in parentheses.

b Calculated by the reviewers from data presented in this table.

* Statistically different from control at $p \leq 0.05$

** Statistically different from control at $p \leq 0.01$

TABLE 4a. Mean (±SE) body weight and food consumption - gestation and lactation, P generation [a]

Observations/study day	Dose Group (ppm)			
	Control	50	300	600
P Generation - Gestation				
Mean body weight (g) GD 0	232.8 ± 3.14	231.7 ± 3.09	222.1 ± 2.99* (↓5)	220.9 ± 3.53* (↓5)
Mean body weight (g) GD 6	255.2 ± 3.70	252.9 ± 4.20	245.2 ± 3.12	243.4 ± 3.20
Mean body weight (g) GD 13	281.4 ± 3.65	277.6 ± 3.70	270.4 ± 3.32	264.3 ± 3.30** (↓6)
Mean body weight (g) GD 20	356.9 ± 4.76	361.2 ± 5.65	351.5 ± 5.86	337.4 ± 3.98** (↓5)
Overall body weight gain (g) GDs 0-20	124.1 ± 4.09	129.6 ± 3.95	129.3 ± 4.03	116.5 ± 3.74
Mean food consumption (g/kg/day) GDs 0-6	81.0 ± 2.48	80.5 ± 1.62	83.1 ± 1.80	79.6 ± 1.68
Mean food consumption (g/kg/day) GDs 6-13	82.3 ± 1.54	80.6 ± 2.36	79.2 ± 1.00	78.6 ± 0.88
Mean food consumption (g/kg/day) GDs 13-20	83.7 ± 1.06	84.0 ± 0.94	85.8 ± 2.17	82.4 ± 1.82
P Generation - Lactation				
Mean body weight (g) LD 0	271.1 ± 5.02	273.3 ± 3.76	264.4 ± 4.44	252.6 ± 3.43* (↓7)
Mean body weight (g) LD 7	297.0 ± 4.37	298.5 ± 3.90	291.0 ± 4.02	277.6 ± 4.19** (↓7)
Mean body weight (g) LD 14	316.1 ± 3.87	315.9 ± 5.77	298.7 ± 6.76	292.1 ± 5.15** (↓8)
Mean body weight (g) LD 21	307.8 ± 3.33	304.6 ± 5.05	297.4 ± 6.48	287.3 ± 5.77** (↓7)
Overall body weight gain (g) [b] LDs 0-21	36.7	31.3	33.0	34.7

a Data obtained from Tables 4, 5, and 6 on pages 57, 60, and 63 in the study report (MRID 44927702); n=21-29. Percent difference from controls (calculated by the reviewers) is included in parentheses.
b Calculated by the reviewers from data presented in this table.
* Statistically different from control at $p \leq 0.05$
** Statistically different from control at $p \leq 0.01$

TABLE 4b. Mean (±SE) body weight and food consumption - gestation and lactation, F_1 generation [a]

Observations/study day	Dose Group (ppm)			
	Control	50	300	600
F_1 Generation - Gestation				
Mean body weight (g) GD 0	244.0 ± 4.15	249.2 ± 3.72	236.0 ± 3.20	223.1 ± 3.57** (↓9)
Mean body weight (g) GD 6	258.7 ± 4.01	265.4 ± 3.98	253.4 ± 3.47	239.2 ± 4.58** (↓8)
Mean body weight (g) GD 13	284.1 ± 4.54	291.8 ± 4.20	276.8 ± 3.36	262.8 ± 3.93** (↓7)
Mean body weight (g) GD 20	364.8 ± 6.93	371.5 ± 6.80	353.0 ± 5.32	337.8 ± 6.50* (↓7)
Overall body weight gain (g) GDs 0-20	120.9 ± 4.79	122.3 ± 3.74	117.0 ± 3.70	114.6 ± 4.44 (↓5)
Mean food consumption (g/kg/day) GDs 0-6	72.8 ± 1.35	72.5 ± 1.12	74.0 ± 2.13	75.5 ± 1.74
Mean food consumption (g/kg/day) GDs 6-13	77.8 ± 0.94	77.4 ± 1.09	80.1 ± 1.48	81.5 ± 1.79
Mean food consumption (g/kg/day) GDs 13-20	81.4 ± 1.09	81.7 ± 1.09	80.5 ± 0.97	82.5 ± 1.06
F_1 Generation - Lactation				
Mean body weight (g) LD 0	277.0 ± 4.41	284.6 ± 4.01	268.3 ± 2.90	252.8 ± 4.55** (↓9)
Mean body weight (g) LD 7	302.6 ± 4.68	308.9 ± 4.33	292.8 ± 3.79	274.4 ± 5.11** (↓9)
Mean body weight (g) LD 14	321.7 ± 4.71	325.7 ± 4.38	309.5 ± 4.45	290.2 ± 5.03** (↓10)
Mean body weight (g) LD 21	307.6 ± 3.79	312.3 ± 4.13	304.5 ± 4.34	291.0 ± 5.30* (↓5)
Overall body weight gain (g) [b] LDs 0-21	30.6	27.7	36.2	38.2

a Data obtained from Tables 4, 5, and 6, pages 58, 61,and 64 in the study report (MRID 44927702); n=23-28. Percent difference from controls (calculated by the reviewers) is presented in parentheses.
b Calculated by the reviewers from data presented in this table.
* Statistically different from control at p≤0.05.
** Statistically different from control at p≤0.01.

3. <u>Test substance intake</u>: Based on food consumption, body weight, and diet analyses data, the mean achieved doses during pre-mating are presented in Table 5. It should be noted that these values may not represent the intake at times such as post weaning growth, gestation and lactation.

TABLE 5. Mean test substance intake during premating (mg/kg body weight/day) [a]

Study interval	Nominal dose (ppm)			
	0	50	300	600
Males	0	3.5	21	41
Females	0	4.2	26	51

a Data were obtained from page 30 in the study report (MRID 44927702). Values are the average of the mean achieved doses for the P and F_1 animals.

4. Reproductive function

a. Estrous cycle length and periodicity: The number of estrous cycles and estrous cycle length of the treated dams were comparable to controls in the P generation and F_1 generation.

b. Sperm measures: Not evaluated.

5. Reproductive performance: No treatment-related effects on reproductive performance (mating, fertility, or gestation indices or gestation length) were observed (Table 6).

TABLE 6. Reproductive performance [a]

Observation	Dose Group (ppm)			
	Control	50	300	600
P Generation				
Mean (±SE) preinsemination interval (days)	2.7 ± 0.22	3.3 ± 0.59	2.6 ± 0.28	3.4 ± 0.68
Number cohoused	30	29	30	30
Number mated	30	29	30	30
Number delivered	28	29	24	27
Intercurrent deaths	1	1	4	3
Mating index (%)	100.0	100.0	100.0	100.0
Fertility index (%)	93.3	100.0	93.3	100.0
Gestation index (%)	100.0	100.0	82.1	90.0
Mean (±SE) gestation length (days)	22.2 ± 0.12	22.3 ± 0.11	22.4 ± 0.17	22.4 ± 0.14
F_1 Generation				
Mean (±SE) preinsemination interval (days)	2.5 ± 0.38	2.2 ± 0.21	2.8 ± 0.21	2.7 ± 0.22
Number cohoused	30	30	30	30
Number mated	30	30	30	30
Number delivered	25	28	26	28
Intercurrent deaths	1	0	1	1
Mating index (%)	100.0	100.0	100.0	100.0
Fertility index (%)	86.7	93.3	86.7	93.3
Gestation index (%)	96.2	100.0	100.0	96.4
Gestation length (days)	22.3 ± 0.14	22.3 ± 0.13	22.3 ± 0.10	22.2 ± 0.13

a Data obtained from page 28 and Table 9 on pages 72 and 73 in the study report (MRID 44927702).

6. Parental postmortem results

a) Organ weights: Absolute and relative (to body weight) liver weights (Table 7a) were increased ($p \leq 0.05$) in the 300 ppm males (↑15-17%) and 600 ppm males and females (↑18-29%) in the P generation. In the F_1 generation parents, terminal body weights were decreased ($p \leq 0.05$) in the 600 ppm males (↓15%) and females (↓5%), and absolute and relative liver weights were increased ($p \leq 0.05$) in the 300 (↑16-18%) and 600 (↑29-36%) ppm females. In the F_1 males, only relative liver weights were increased (↑20%; $p \leq 0.05$) at 600 ppm, while absolute liver weights were comparable to controls.

Absolute and relative (to body weight) thyroid weights (Table 7b) were increased ($p \leq 0.05$) in the

300 ppm females (↑14-23%) and 600 ppm males and females (↑21-26%) in the P generation. In the F_1 generation parents, relative thyroid weights were increased ($p \leq 0.05$) in the 300 ppm males (↑16%) and 600 ppm males and females (↑16-22%), while absolute thyroid weights were comparable to controls.

In the F_1 generation, increases ($p \leq 0.05$) were noted in relative (to body weight) testes weight (↑22%) and ovary weight (↑14%). However, these increases were most likely due to the decreased terminal body weight in these animals because absolute weights of these organs were comparable to controls, and there were no macroscopic or microscopic findings to corroborate an effect of treatment in these organs. All other absolute and relative organ weights were comparable to controls in the P and F_1 parents.

TABLE 7a. Absolute and relative (to body weight) liver weights (mean±SD) [a]

Parameters	Dose Group (ppm)			
	Control	50	300	600
P Generation Males				
Terminal body weight (g)	405.6 ± 45.7	413.0 ± 37.2	411.4 ± 39.2	407.2 ± 39.8
Absolute liver weight (g)	17.431 ± 2.664	18.526 ± 3.564	20.365 ± 3.304* (↑17)	22.408 ± 3.671* (↑29)
Relative liver weight (%)	4.294 ± 0.421	4.467 ± 0.602	4.936 ± 0.525* (↑15)	5.500 ± 0.684* (↑28)
P Generation Females				
Terminal body weight (g)	290.7 ± 24.1	288.7 ± 25.0	279.5 ± 30.1	281.6 ± 30.8
Absolute liver weight (g)	16.631 ± 2.986	16.883 ± 2.272	17.420 ± 4.125	19.700 ± 3.119* (↑18)
Relative liver weight (%)	5.710 ± 0.884	5.856 ± 0.721	6.187 ± 1.146	7.023 ± 1.043* (↑23)
F_1 Generation Males				
Terminal body weight (g)	446.6 ± 42.6	424.5 ± 31.2	432.2 ± 42.0	379.8 ± 26.9* (↓15)
Absolute liver weight (g)	20.303 ± 4.162	18.916 ± 2.530	20.936 ± 3.020	20.628 ± 2.886
Relative liver weight (%)	4.520 ± 0.674	4.457 ± 0.519	4.844 ± 0.501	5.426 ± 0.593* (↑20)
F_1 Generation Females				
Terminal body weight (g)	291.5 ± 21.3	298.5 ± 22.2	285.8 ± 23.2	276.1 ± 28.0* (↓5)
Absolute liver weight (g)	16.213 ± 3.200	17.758 ± 2.833	18.815 ± 3.946* (↑16)	20.934 ± 3.926* (↑29)
Relative liver weight (%)	5.542 ± 0.959	5.946 ± 0.867	6.538 ± 1.070* (↑18)	7.548 ± 1.016* (↑36)

a Data obtained from Table OW1K-SUM on pages 403-406 in the study report (MRID 44927702). Percent difference from controls is presented in parentheses; n=26-30.

* Statistically different from control, $p \leq 0.05$

TABLE 7b. Absolute and relative (to body weight) thyroid weights (mean ± SD) [a]

Parameters	Dose Group (ppm)			
	Control	50	300	600
P Generation Males				
Terminal body weight (g)	405.6 ± 45.7	413.0 ± 37.2	411.4 ± 39.2	407.2 ± 39.8
Absolute thyroid weight (g)	0.020 ± 0.004	0.020 ± 0.005	0.022 ± 0.006	0.025 ± 0.007* (↑25)
Relative thyroid weight (%)	0.0049 ± 0.0011	0.0049 ± 0.0009	0.0055 ± 0.0014	0.0061 ± 0.0015* (↑24)
P Generation Females				
Terminal body weight (g)	290.7 ± 24.1	288.7 ± 25.0	279.5 ± 30.1	281.6 ± 30.8
Absolute thyroid weight (g)	0.014 ± 0.004	0.014 ± 0.003	0.016 ± 0.003* (↑14)	0.017 ± 0.004* (↑21)
Relative thyroid weight (%)	0.0047 ± 0.0013	0.0049 ± 0.0010	0.0058 ± 0.0014* (↑23)	0.0059 ± 0.0015* (↑26)
F_1 Generation Males				
Terminal body weight (g)	446.6 ± 42.6	424.5 ± 31.2	432.2 ± 42.0	379.8 ± 26.9* (↓15)
Absolute thyroid weight (g)	0.022 ± 0.005	0.021 ± 0.007	0.025 ± 0.006	0.023 ± 0.005
Relative thyroid weight (%)	0.0050 ± 0.0014	0.0050 ± 0.0014	0.0058 ± 0.0015* (↑16)	0.0061 ± 0.0013* (↑22)
F_1 Generation Females				
Terminal body weight (g)	291.5 ± 21.3	298.5 ± 22.2	285.8 ± 23.2	276.1 ± 28.0* (↓5)
Absolute thyroid weight (g)	0.016 ± 0.004	0.017 ± 0.003	0.017 ± 0.003	0.018 ± 0.004
Relative thyroid weight (%)	0.0056 ± 0.0012	0.0057 ± 0.0012	0.0060 ± 0.0013	0.0065 ± 0.0015* (↑16)

a Data obtained from Table OW1K-SUM on pages 403-406 in the study report (MRID 44927702). Percent difference from controls is presented in parentheses; n=26-30.

* Statistically different from control, $p \leq 0.05$

b) Pathology

1) Macroscopic examination: Dystocia was noted in the 300 and 600 ppm P dams (Table 8). Paleness and stained/wet ventrum were associated with dystocia in these animals. No treatment-related gross pathological findings were noted in the F_1 parental animals.

TABLE 8. Selected macroscopic findings in the P generation dams (# affected animals) [a]

Parameters	Dose Group (ppm)			
	0	50	300	600
Dystocia	0	0	3	2
Pale	0	0	1	2
Ventrum wet/stained	0	0	3	3

a Data obtained from Table GP1-SUM on pages 357-358 in the study report; n=30

2) Microscopic examination: Increased ($p \leq 0.05$) incidences of hepatocytomegaly were observed in the 300 and 600 ppm males and females in the P and F_1 generations (Tables 9a and 9b). Average severity (minimal to slight) of this finding was also increased in a dose-dependent manner. Additionally, dose-dependent increases (not significant) in the incidence and severity (minimal to moderate) of necrosis were observed in the liver in the P females. Incidences of thyroid follicular cell hypertrophy were increased ($p \leq 0.05$) in the 300 ppm females and 600 ppm males and females. Average severity (minimal to slight) of follicular cell hypertrophy was dose-dependently increased in the F_1 generation. No other treatment-related microscopic findings were noted.

TABLE 9a. Selected histopathological findings in the P generation dams [a] [# affected animals (average severity)] [b]

Parameters		Dose Group (ppm)			
		0	50	300	600
Males					
Liver -	hepatocytomegaly	0 (0.0)	0 (0.0)	10 (1.0)*	28 (1.5)*
Thyroid -	follicular cell hypertrophy	5 (1.0)	4 (1.0)	7 (1.0)	20 (1.0)*
Females					
Liver -	hepatocytomegaly	0 (0.0)	0 (0.0)	10 (1.0)*	26 (1.8)*
	necrosis	0 (0.0)	0 (0.0)	4 (1.8)	3 (2.3)
Thyroid -	follicular cell hypertrophy	0 (0.0)	0 (0.0)	5 (1.0)*	17 (1.0)*

a Data obtained from Table MP1-SUM, pages 408-413 in the study report; n = 30.
b Average severity is based upon a five point scale: minimal (1), slight (2), moderate (3), moderately severe (4), and severe (5).
* Statistically different from control, $p \leq 0.05$

TABLE 9b. Selected histopathological findings in the F_1 generation dams [a] [# affected animals (average severity)] [b]

Parameters	Dose (ppm)			
	0	50	300	600
Males				
Liver - hepatocytomegaly	0 (0.0)	0 (0.0)	18 (1.1)*	27 (1.8)*
Thyroid - follicular cell hypertrophy	6 (1.0)	7 (1.0)	13 (1.0)	19 (1.2)*
Females				
Liver - hepatocytomegaly	0 (0.0)	0 (0.0)	16 (1.0)*	29 (1.9)*
Thyroid - follicular cell hypertrophy	4 (1.0)	4 (1.0)	18 (1.0)*	25 (1.1)*

a Data obtained from Table MP1-SUM, pages 414-418 in the study report; n = 29-30.
b Average severity is based upon a five point scale: minimal (1), slight (2), moderate (3), moderately severe (4), and severe (5).
* Statistically different from control, $p \leq 0.05$

B. OFFSPRING

1. Viability and clinical signs: Litter data for the F_1 and F_2 generations are presented in Table 10. The live birth index was decreased (not significant) at 600 ppm in the F_1 (91.0% treated vs 99.1% controls) and F_2 (90.2% treated vs 95.8% controls) generations and was lower than the range of historical controls (97-100% each generation). Additionally in the F_1 generation pups, the viability index (days 0-4) was decreased (not significant) at 600 ppm (82.8% treated vs 97.4% controls) and was lower than the range of historical controls (91-99%). The number of stillborn pups was increased in all treated F_1 groups (2, 16, 13, and 16 in the 0, 50, 300, and 600 ppm groups, respectively) and exceeds the range of historical controls (0-13) at 50 and 600 ppm but there was no dose response. There were no treatment-related clinical signs in the pups of the F_1 or F_2 generations.

TABLE 10. Litter parameters for F1 and F2 generations [a]

Observation	Dose Group (ppm)			
	Control	50	300	600
F_1 Generation				
Mean (±SE) implantation sites	12.6 ± 0.50	13.6 ± 0.37	13.4 ± 0.29	12.1 ± 0.46
Number born live [b]	312	344	277	266
Number born dead	2	16	13	16
Mean (±SE) sex ratio (% ♂)	57.1 ± 3.28	53.4 ± 3.26	50.7 ± 2.97	51.1 ± 3.69
# Deaths Days 0-21	NR	NR	NR	NR
# Deaths Days 4-21	NR	NR	NR	NR
# Deaths Days 0-21	4	16	16	10
Mean (±SE) litter size Day 0	11.2 ± 0.56	12.4 ± 0.40	12.1 ± 0.61	10.4 ± 0.48
Day 4 [c]	11	11	12	10
Day 4 [d]	8	7	8	8
Day 7 [e]	7.6	7.4	6.9	6.9
Day 14 [e]	7.6	7.4	6.9	6.9
Day 21	8	8	8	8
Birth index (mean±SE)	87.3 ± 2.99	91.0 ± 1.54	89.8 ± 3.86	85.9 ± 2.40
Live birth index (mean±SE)	99.1 ± 0.48	95.8 ± 1.72	94.9 ± 4.24	91.0 ± 3.26
Viability (Days 0-4) index (mean±SE)	97.4 ± 1.03	91.5 ± 3.91	89.9 ± 5.95	82.8 ± 6.39
Lactation index (mean±SE)	99.6 ± 0.45	96.6 ± 3.45	98.8 ± 0.82	99.5 ± 0.52
F_2 Generation				
Mean (±SE) implantation sites	12.6 ± 0.76	13.0 ± 0.53	12.9 ± 0.44	12.2 ± 0.65
Number born live [b]	297	333	310	295
Number born dead	9	14	8	18
Mean (±SE) sex ratio (% ♂)	44.1 ± 2.85	53.2 ± 2.17	48.5 ± 2.55	52.5 ± 2.23
# Deaths Days 0-4	NR	NR	NR	NR
# Deaths Days 4-21	NR	NR	NR	NR
# Deaths Days 0-21	7	4	9	8
Mean (±SE) litter size Day 0	12.2 ± 0.83	12.4 ± 0.55	12.2 ± 0.51	11.2 ± 0.68
Day 4 [c]	12	12	11	10
Day 4 [d]	8	8	8	7
Day 7 [e]	7.4	7.5	7.6	6.9
Day 14 [e]	7.4	7.5	7.5	6.9
Day 21	8	8	8	7
Birth index (mean±SE)	94.4 ± 1.53	93.0 ± 1.49	93.3 ± 2.09	90.5 ± 2.69
Live birth index (mean±SE)	95.8 ± 2.79	95.9 ± 1.78	96.6 ± 1.28	90.2 ± 4.18
Viability (Days 0-4) index (mean±SE)	93.9 ± 4.20	98.1 ± 1.38	94.5 ± 2.79	91.6 ± 3.48
Lactation index (mean±SE)	99.0 ± 0.68	99.6 ± 0.45	98.1 ± 0.90	98.1 ± 1.85

a Data obtained from Tables 9 and 10 on pages 72-78 in the study report (MRID 44927702).
b Calculated by the reviewers by subtracting the number of stillborn pups from the total number of pups born.
c Before standardization (culling)
d After standardization (culling)
e Calculated by the reviewers from individual data in Appendix XVI on pages 294-325.
NR Not reported

2. Body weight: Mean pup body weight data are presented in Table 11. At 600 ppm, pup weights were decreased ($p \leq 0.05$) in the F_1 (↓8-15%) and F_2 (↓11-20%) litters beginning on PND 7; the magnitude of the decrease compared to controls was more pronounced as lactation

proceeded. At 300 ppm, pup weights were decreased (↓8-9%; $p \leq 0.05$) after PND 14 in the females of the F_1 generation and in the males and females of the F_2 generation. No differences in pup weights were observed at 50 ppm.

TABLE 11. Mean (±SE) litter and pup weights (g) [a]

Post-natal Day	Dose Group (ppm)							
	0	50	300	600	0	50	300	600
	F_1 Litters				F_2 Litters			
0	6.6	6.7	6.5	6.5	6.6	6.6	6.6	6.4
4 [b]	10.2	10.0	9.8	9.5	10.1	10.5	9.7	9.3
4 [c]	10.2	10.0	9.8	9.5	10.1	10.5	9.7	9.3
7	15.4	15.6	15.0	14.1*(↓8)	15.6	16.1	14.8	13.9**(↓11)
14	29.5	29.6	27.4	25.4**(↓14)	30.5	31.2	27.9**(↓9)	25.8**(↓15)
21	47.7	48.7	43.9	40.7**(↓15)	50.2	49.5	45.7*(↓9)	40.1**(↓20)
	F_1 Pups - male				F_2 Pups - male			
0	6.8±0.08	6.9±0.09	6.7±0.11	6.6±0.14	6.8±0.13	6.8±0.11	6.8±0.06	6.5±0.10
4 [b]	10.4±0.25	10.2±0.27	10.0±0.21	9.7±0.27	10.2±0.33	10.7±0.28	10.0±0.18	9.5±0.37
4 [c]	10.3±0.25	10.2±0.27	10.0±0.21	9.7±0.27	10.2±0.33	10.7±0.27	10.0±0.19	9.6±0.36
7	15.7±0.41	15.8±0.36	15.3±0.29	14.3±0.35* (↓9)	15.8±0.39	16.4±0.36	15.2±0.27	14.2±0.47* (↓10)
14	30.0±0.85	30.0±0.56	27.9±0.62	25.8±0.66** (↓14)	30.9±0.59	31.9±0.50	28.5±0.49** (↓8)	26.3±0.65** (↓15)
21	48.5±1.57	49.5±0.99	44.6±1.20	41.2±1.15** (↓15)	51.1±1.19	50.5±1.02	46.6±1.06* (↓9)	41.2±1.39** (↓19)

(table continues next page)

Post-natal Day	Dose (ppm)							
	0	50	300	600	0	50	300	600
	F_1 Pups - female				F_2 Pups - female			
0	6.4±0.10	6.5±0.08	6.3±0.09	6.3±0.12	6.4±0.12	6.4±0.10	6.4±0.06	6.2±0.11
4 [b]	9.9±0.26	9.7±0.22	9.6±0.19	9.3±0.27	10.0±0.30	10.2±0.29	9.4±0.15	9.1±0.35
4 [c]	9.9±0.27	9.7±0.22	9.6±0.19	9.3±0.28	10.0±0.31	10.2±0.29	9.4±0.15	9.1±0.34
7	15.2±0.39	15.3±0.37	14.8±0.25	13.9±0.36* (↓9)	15.4±0.37	15.7±0.40	14.5±0.26	13.6±0.44** (↓12)
14	29.4±0.54	29.2±0.58	27.0±0.57* (↓8)	25.2±0.67** (↓14)	30.1±0.52	30.4±0.56	27.4±0.54** (↓9)	25.5±0.59** (↓15)
21	47.5±0.90	47.8±1.10	43.1±1.11* (↓9)	40.2±1.17** (↓15)	49.2±1.13	48.4±1.03	44.7±1.07* (↓9)	39.3±1.33** (↓20)

a Data obtained from Tables 10 and 12 on pages 75, 77, and 83-88 in the study report (MRID 44927702). Percent difference from the controls, calculated by the reviewers, is included in parentheses.
b Before standardization (culling)
c After standardization (culling)
* Statistically different from control, $p \leq 0.05$
** Statistically different from control, $p \leq 0.01$

3. Sexual maturation (F_1): Not evaluated.

4. Offspring postmortem results

a) Organ weights: Pup organs were not weighed.

b) Pathology

1) Macroscopic examination: No treatment-related gross pathological findings were noted in the F_1 or F_2 pups.

2) Microscopic examination: Microscopic examinations were not performed.

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS: The reproductive toxicity NOEL for YRC 2894 was 50 ppm, based on the possible compound-induced dystocia in the 300 and 600 ppm dose groups. The neonatal NOEL was 50 ppm, based on a possible compound-induced decrease in the live birth index in the 600 ppm dose group and decreased pup body weights in the 300 and 600 ppm dose groups. The parental toxicity NOEL was 50 ppm, based on: (i) lower adult male and/or female premating body weights in the 600 ppm dose groups; (ii) lower gestation body weights in the 600 ppm dose group; (iii) lower lactation body weights in the 600 ppm dose group; and (iv) liver and thyroid gross pathology and micropathology findings in the 300 ppm and 600 ppm dose

groups.

B. CONTRACTOR REVIEWER COMMENTS

1. PARENTAL ANIMALS: In the P generation, four dams at 300 ppm and 3 dams at 600 ppm were found dead or sacrificed on GD 23-24 because of dystocia. Paleness and stained/wet ventrum were associated with dystocia in these animals. It was stated that because dystocia is historically not a common finding, further studies are being conducted to investigate the possible mechanism(s) by which dystocia is induced by treatment.

In the P females, body weights were decreased (↓4-8%; $p \leq 0.05$) at 600 ppm during the last three weeks of premating and throughout gestation (except on GD 6) and lactation. Additionally, body weights were decreased (↓5%; $p \leq 0.05$) in the 300 ppm females at GD 0.

In the 600 ppm F_1 animals, no evidence of dystocia was noted. Body weights were decreased ($p \leq 0.05$) in the males throughout the study (↓14-19%) and in the females throughout premating (↓8-10%), gestation (↓7-9%), and lactation (↓5-10%). Food consumption was increased (↑5-9%; $p \leq 0.05$) during premating in the males at this dose during weeks 2-12 (except week 11) and in the females during weeks 2, 5, and 8-10. Additionally in the 300 ppm males, food consumption was increased (↑5-7%; $p \leq 0.05$) during weeks 8 and 10.

Absolute and relative (to body weight) liver weights were increased ($p \leq 0.05$) in the 300 ppm males (↑15-17%) and 600 ppm males and females (↑18-29%) in the P generation. In the F_1 generation parents, terminal body weights were decreased ($p \leq 0.05$) in the 600 ppm males (↓15%) and females (↓5%), and absolute and relative liver weights were increased ($p \leq 0.05$) in the 300 (↑16-18%) and 600 (↑29-36%) ppm females. In the males in this generation, only relative liver weights were increased (↑20%; $p \leq 0.05$) at 600 ppm, while absolute liver weights were comparable to controls. Although increased relative liver weights alone could be attributed to decreased terminal body weights in the F1 males, these increases were considered treatment-related because of the corroborating histopathology. Increased ($p \leq 0.05$) incidences of hepatocytomegaly were observed in the 300 and 600 ppm males and females in the P and F_1 generations. Average severity (minimal to slight) of this finding was also increased in a dose-dependent manner. Additionally, dose-dependent increases (not significant) in the incidence and severity (minimal to moderate) of necrosis were observed in the liver in the P females.

Absolute and relative (to body weight) thyroid weights were increased ($p \leq 0.05$) in the 300 ppm females (↑14-23%) and 600 ppm males and females (↑21-26%) in the P generation. In the F_1 generation parents, relative thyroid weights were increased ($p \leq 0.05$) in the 300 ppm males (↑16%) and 600 ppm males and females (↑16-22%), while absolute thyroid weights were comparable to controls. Again, while the increased relative thyroid weights alone could be attributed to the decreased terminal body weights, the increases in relative thyroid weights in the F_1 generation were considered treatment-related because of the corroborating histopathology. In both generations, incidences of thyroid follicular cell hypertrophy were increased ($p \leq 0.05$) in the 300 ppm females and 600 ppm males and females. Average severity (minimal to slight) of follicular cell hypertrophy was dose-dependently increased in the F_1 generation.

No treatment-related findings were noted at 50 ppm.

The LOAEL for parental toxicity is 300 ppm based on increased liver and thyroid weights and on hepatocytomegaly, liver necrosis, and thyroid follicular cell hypertrophy. The NOAEL is 50 ppm.

2. OFFSPRING: The live birth index was decreased (not significant) at 600 ppm in the F_1 (91.0% treated vs 99.1% controls) and F_2 (90.2% treated vs 95.8% controls) generations and was lower than the range of historical controls (97-100% each generation). The number of stillborn pups was increased in all treated F_1 groups (2, 16, 13, and 16 in the 0, 50, 300, and 600 ppm groups, respectively) and exceeds the range of historical controls (0-13) at 50 and 600 ppm. Additionally in the F_1 pups, the viability index (days 0-4) was decreased (not significant) at 600 ppm (82.8% treated vs 97.4% controls) and was lower than the range of historical controls (91-99%). The Sponsor stated that this decreased viability was due to an increased number of cannibalized pups at the high dose. The data show that there was an increased number of cannibalized pups and missing pups (presumed cannibalized) at 600 ppm (17 pups/7 litters treated vs 5 pups/4 litters controls); however, it is possible that the pups were dead before cannibalization. Therefore, a treatment-related effect on viability cannot be excluded.

At 600 ppm, pup weights were decreased ($p \leq 0.05$) in the F_1 (↓8-15%) and F_2 (↓10-20%) litters after PND 7; the magnitude of the decrease compared to controls was more pronounced as lactation proceeded. At 300 ppm, pup weights were decreased (↓8-9%; $p \leq 0.05$) after PND 14 in the females of the F_1 generation and in the males and females of the F_2 generation.

No treatment-related findings were noted at 50 ppm.

The LOAEL for offspring toxicity is 300 ppm based on decreased pup weight. The NOAEL is 50 ppm.

The LOAEL for reproductive performance is 300 ppm based on dystocia. The NOAEL for reproductive performance is 50 ppm.

The reproductive study in the rat is **acceptable/guideline** and satisfies the requirements for a two-generation reproduction study (OPPTS 870.3800; OECD 416) in the rat.

C. STUDY DEFICIENCIES:

- Developmental landmarks and organ weights were not evaluated in the F_1 or F_2 offspring.
- Sperm enumeration, motility, and morphology were not determined in the P and F_1 parental males.

DATA FOR ENTRY INTO ISIS

Reproductive Study - rats (870.3800)

PC code	MRID #	Study type	Species	Duration	Route	Dosing method	Dose range mg/kg	Doses tested mg/kg	NOAEL mg/kg	LOAEL mg/kg	Endpoint(s)	Comments
014019	44927702	reproductive	rats	2 generat	oral	diet	3.5-51	0/0, 3.5/4.2, 21/26, 41/51 in M/F	3.5	21	liver, thyroid	Parental/ systemic
014019	44927702	reproductive	rats	2 generat	oral	diet	3.5-51	0/0, 3.5/4.2, 21/26, 41/51 in M/F	3.5	21	pup weights	Offspring
014019	44927702	reproductive	rats	2 generat	oral	diet	3.5-51	0/0, 3.5/4.2, 21/26, 41/51 in M/F	3.5	21	dystocia	Reproductive

APPENDIX

Range-finding study for a two-generation reproduction toxicity study

Since this is a range-finding study, only a summary is provided to confirm the adequacy of the dose selection rationale used in subsequent studies.

In a two-generation reproduction range-finding study (MRID 44927638), YRC 2894 (thiacloprid; 98.6% a.i.; Lot/batch #NLL 3351-13) was administered continuously in the diet to Crl:CD BR rats (7/sex/dose) at nominal dose levels of 0, 100, 400, or 1600 ppm. The P animals were given test article diet formulations beginning 4 weeks prior to mating to produce the F_1 litters. F_1 animals were euthanized in 3 stages: (1) All but 4 pups/sex/litter (where possible) were euthanized on post-natal day (PND) 4; (2) 3 additional pups/sex/litter were sacrificed on PND 21; and (3) the remaining 1 pup/sex/litter was retained until PND 35. All P adults, 1 pup/sex/litter of the F_1 generation, and animals that died were necropsied, and the liver and thyroids were examined microscopically.

In the 1600 ppm P animals, body weights were decreased ($p \leq 0.05$) throughout premating in the males (↓10-13%) and females (↓9-11%), throughout gestation (↓10-13%), and during the first half of lactation (↓10-11%). Overall body weight gains were decreased ($p \leq 0.01$) during premating in the males (↓39%) and females (↓48%), were decreased (not significant) during gestation (↓20%), and were increased ($p \leq 0.01$) during lactation (↑173%). An initial decrease (↓43-53%; $p \leq 0.05$) in food consumption was observed in the males and females during the first week of premating. Food consumption was also sporadically decreased ($p \leq 0.05$) in the males on premating day 25 (↓15%) and in the females on GD 7 (↓17%).

For the 1600 ppm F_1 litters, the number of stillborn pups was increased ($p \leq 0.05$) at this dose (21.6% treated vs 8.4% controls). The median viability index of these pups was decreased ($p \leq 0.01$) to 90.9% from 100% in controls, and the mean viability index was decreased (not significant) to 83.9% from 96.4% in controls due to the increase in pup deaths (16 treated vs 3 controls). Pup weights were decreased (↓17-28%; $p \leq 0.05$) beginning on PND 4, and overall (PND 0-35) body weight gains were decreased (↓28%; $p \leq 0.01$).

All males and females at 1600 ppm in the P and F_1 generations and one P generation female at 400 ppm had changes in the liver suggestive of hepatotoxicity, including hepatocellular hypertrophy, ground-glass-like cytoplasm, fine cytoplasmic vacuolation (exaggerated foamy appearance), eosinophilic cytoplasmic inclusions, and increased mitotic figures. Subtle changes in the thyroid follicles (taller appearance resulting in smaller follicular lumina) were observed in four males and 6 females at 1600 ppm and one male at 400 ppm in the P generation and 4 high-dose rats of the F_1 generation.

No treatment-related findings were noted at 100 ppm.

The reproductive range-finding toxicity study is **acceptable/non-guideline** and satisfies the requirements for which is was intended as a dose-selection rationale.

The LOAEL for parental toxicity is 400 ppm based on microscopic findings in the liver and thyroid. The NOAEL is 100 ppm.

COMPLIANCE: Signed and dated Data Confidentiality, GLP, Flagging, and Quality Assurance statements were provided.