FINAL

DATA EVALUATION REPORT

IMIDACLOPRID

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 Pia Lindström Date 5/24/93
Pia Lindström, DPH

Independent Reviewer Sanjay Diwan Date 6/24/93
Sanjay Diwan, Ph.D.

QA/QC Manager Sharon Segal Date 3/25/93
Sharon Segal, Ph.D.

Contract Number: 68D10075
Work Assignment Number: 2- 66
Clement Number: 189
Project Officer: Caroline Gordon

EPA Reviewer: Myron Ottley, Ph.D.
Review Section IV, Toxicology Branch I/HED

Signature: MOttley
Date: 7/2/93

EPA Section Head: Marion Copley, D.V.M.
Review Section I, Toxicology Branch I/HED

Signature: Marion Copley
Date: 7/7/93

DATA EVALUATION REPORT

STUDY TYPE: Reproductive toxicity; Guideline Series 83-4

EPA IDENTIFICATION NUMBERS

PC Code: 129099

TOX CHEM. NUMBER.: 497E

MRID NUMBER.: 422563-40

TEST MATERIAL: 1-[(6-chloro-3-pyridinyl)methyl]-4,5-dihydro-N-nitro-1H-imidazol-2-amine

SYNONYMS: Imidacloprid; NTN 33893

SPONSOR: Bayer Ag, Wuppertal, Germany

STUDY NUMBER: 100647

TESTING FACILITY: RCC, Research and Consulting Company AG, Itingen, Switzerland

TITLE OF REPORT: NTN 33893 Technical (Proposed C.N. Imidacloprid) Multiple Generation Reproduction Study in Rats

AUTHORS: P. Suter, K. Bierdermann, H. Luetkemeier, J.TH. Wilson, CH. Terrier

REPORT ISSUED: June 21, 1990

CONCLUSIONS: In a two-generation reproduction study, Wistar/Han rats were fed Imidacloprid in the diet at dosage levels of 0, 100, 250, or 700 ppm (during premating at 100, 250, and 700 ppm, for males ≈7.3, ≈18.3, and ≈52.0 mg/kg/day and for females ≈8.0, ≈20.5, and ≈57.4 mg/kg/day, respectively).

Parental NOEL = 700 ppm (≈55 mg/kg/day)
LOEL = Not determined

Reproductive NOEL = 100 ppm (≈ 8 mg/kg/day)
LOEL = 250 ppm (≈19 mg/kg/day), based on decreased pup body weight in both generations.

CLASSIFICATION: CORE Minimum Data. This study meets the minimum requirements set forth under Guideline Series 83-4 for a two-generation reproductive toxicity study in rats. The study has been classified as Minimum Data owing

to the following reporting deficiencies: No protocol was submitted and data supporting the stability of the test compound in the diet were not submitted (see page 8).

A. MATERIALS

Test Compound

Purity:	95.3%
Description:	Solid
Batch number:	Mischpartie 180587
Date received:	Not reported
Contaminants:	None reported

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

Test Animals

Species:	Rat
Strain:	Wistar/HAN
Source:	KFM, Kleintierfarm Madoerin AG, Fuellinsdorf, Switzerland
Age:	4 weeks at delivery
Weight:	F_0 males--123-169 g at study initiation
	F_0 females--81-137 g at study initiation

B. STUDY DESIGN

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

Mating: After 10 days of acclimatization followed by 84 days of dietary treatment, F_0 females were mated with males from the same group in a ratio of 1:1 until a plug or sperm was detected in a vaginal smear (or for a maximum of 22 days). After delivery of the F_{1A} pups, F_0 females were rested for two weeks and then mated again. During the second mating animals were paired with alternative partners. When possible, previously non-pregnant females and males failing to induce pregnancy were paired with previously successfully mated animals. Females, in which no evidence of mating was observed after 22 days, were paired a second time with alternative partners for a period of 22 days (maximum).

Following 105 days of dietary treatment, F_1 animals were paired one male to one female for a maximum of 21 days (sibling matings were avoided). Females in which no evidence of mating was observed were paired for a second time with alternative partners for a maximum of 4 days.

Environmental conditions: Temperature and humidity were maintained at 22°± 3°C and 40%-70%, respectively. There were 10-15 air changes per hour and a 12/12 hour light/dark cycle was maintained.

Group arrangement: F_0 animals were distributed using a random algorithm (computer-generated). F_1 animals were selected randomly according to RCC SOP. The groups were assigned 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	30	30	26	26
Low dose	100	30	30	26	26
Mid dose	250	30	30	26	26
High dose	700	30	30	26	26

Dosage administered: The test material was administered in the diet (Kliba 343 rat/mouse maintenance diet, Klingentalmuehle Ag) for two consecutive generations. Diets were prepared at least every 2 weeks and stored at room temperature. The test material was mixed with granulated food in a Buehler mixer and pelleted in a Buehler pelleting machine. Water (1:10 volume/weight ratio) was used to achieve proper pelleting. Pellets were dried using warm air for 48-96 hours before storage. Analysis for concentration and homogeneity was performed prior to the start of the study, at the start of the prepairing and mating periods, and at the end of the gestation periods. Analysis for stability had been conducted in a previous study (RCC Project 087052).

Dosage rationale: Dosages were selected based upon a range-finding study (RCC Project 087052). The results of this study were not presented.

Observations: Observations for mortality, moribundity, and clinical signs of toxicity were conducted at least twice daily. Body weight data were recorded weekly for both males and females during premating but were not recorded during the mating periods. F_0 and F_1 females were weighed weekly during gestation. F_0 females were weighed on days 0, 4, 7, 14 and 21 postpartum and F_1 females were weighed on days 1, 4, 7, 14 and 21 postpartum. Male body weight data were recorded weekly for the remainder of the study. Food consumption data were recorded weekly with the exception of the mating periods. During the lactation period, food consumption data were only recorded until day 14 postpartum.

The following data were recorded for each litter:

- Number of live and dead pups, sex, and pup weight at birth and on lactation days 1, 4, 7, 14, and 21

- Gross and behavioral abnormalities

Uteri of apparently non-pregnant females were stained according to the method described by Salewski (1964) to detect early embryonic loss.

On day 4, pups were randomly culled to 4/sex/litter whenever possible. Culled pups and pups dying or killed during lactation were examined externally then sacrificed and examined for visceral abnormalities.

Twenty-six male and twenty-six female F_1 pups were randomly selected as F_1 parental animals. All F_1 pups not selected for the F_1 parental group or selected for histopathological examination were sacrificed and subjected to gross examination.

Parental animals of both generations and one pup/sex/generation/group were sacrificed and necropsied after weaning. The following tissues were preserved in 4% neutral phosphate buffered formaldehyde solution. Histopathology was carried out on these organs from the control and high-dose groups. Organs marked with an asterisk (*) were also weighed.

- Uterus
- Cervix
- Pituitary gland
- Prostate gland
- Gross lesions
- Thyroid gland
- *Liver
- *Ovaries
- Seminal vesicles w/coagulation gland
- *Testes w/epididymides
- Vagina

Statistical analysis: The following analyses were conducted.

- Body weight, food consumption, organ weights, clinical chemistry and hematology--ANOVA and Dunnett's test
- Reproductive parameters-- ANOVA based on Wilcoxon's ranks and Kruskall-Wallis' test
- Pup mortality--Fisher's exact test

Hematology and Clinical Chemistry: Blood samples were collected from 10 randomly selected animals/group/sex from the F_1 generation prior to necropsy. Blood samples were drawn from the retro-orbital plexus. Liver samples were also taken from these same animals to assay for triglycerides, cytochrome P-450, and N- and O-demethylase activity. The following parameters were determined:

Hematology

Erythrocyte count (RBC)
Hemoglobin (HB)
Hematocrit (HCT)
Mean corpuscular volume (MCV)
Mean corpuscular hemoglobin (MCH)
Mean corpuscular hemoglobin (PTT)
concentration (MCHC)
Nucleated erythrocytes
normoblasts (NEN)

Total leukocyte count (WBC)
Differential leukocyte count
Red cell morphology
Thromboplastin time (PT)
Partial thromboplastin time
Platelet count (PLATELETS)
Reticulocyte count (RETIC.)

Clinical Chemistry

Electrolytes	Enzymes
Calcium	Aspartate aminotransferase
Chloride	Gamma glutamyl transferase
Potassium	Alanine aminotransferase
Phosphorus	Alkaline phosphatase
Sodium	Creatinine kinase
	Lactate dehydrogenase

Other	In Liver Tissue
Glucose	Triglycerides
Urea nitrogen	Cytochrome P-450
Creatinine	N-demethylase
Globulin	O-demethylase
A/G ratio	
Albumin	
Total protein	
Total cholesterol	
Total bilirubin	
Triglycerides	
Total lipids	
Phospholipids	

Compliance:

- A signed Statement of No Data Confidentiality Claim, dated February 15, 1991, was provided.
- A signed Statement of Compliance with EPA, OECD, Japanese, and Swiss GLPs dated July 3, 1990 and February 15, 1991, was provided.
- A signed Quality Assurance Statement, dated January 22, 1990, was provided.

C. RESULTS

Test Material Analysis

Concentration and homogeneity analyses revealed concentrations from 81.4% to 111.1% of target. The study authors claim that the test material is stable for 21 days based on the results of a previous study (RCC Project 087052). However, results of this study were not presented.

Parental Toxicity

Mortality: No compound-related mortalities were observed in either sex or generation. Incidental deaths/moribund sacrifices are described below.

In the F_0 generation, one female from the control group was found dead on day 38 of the premating period. Necropsy revealed pelvic dilation and

kidneys, ureter, and bladder were filled with a yellowish turbid fluid. Another female from this same group was sacrificed moribund on day 21 of the F_{1B} gestation period. Necropsy revealed collapsed lungs, reduced spleen size, and colon and ceceum distended with gas. A third female at 100 ppm was found dead on day 36 of the premating period. Necropsy revealed advanced autolysis and dilated bladder.

In the F_1 generation, one male at 100 ppm died following blood sampling. Necropsy did not reveal any abnormalities. One male at 250 ppm was sacrificed moribund on day 14 of the F_{2B} postmating period. Necropsy revealed reduced spleen size and red-brown eschar and sores on the lips.

Clinical observations: No compound-related clinical signs were observed in either sex or generation. No summary data were provided. Hair loss and wounds were common findings in all groups (as stated in the text).

Body weight: Compound-related effects in body weight were observed at 700 ppm. Summaries of body weight and weight gain data for selected intervals are presented in Tables 1, 2, and 3. Detailed results are discussed below.

In the F_0 generation, among males at 700 ppm, body weight was significantly lower (5%-9%; Table 1) than control from day 8 of premating through day 56 of postmating, with the exception of days 22 and 29 postmating when the reduction in body weight was not significant (data not shown). Body weight gain was also 10% lower than control among males at 700 ppm on days 1-84 of the premating period.

Among F_0 females, body weight at 700 ppm was significantly lower than control on days 29, 36, 43, 57, 71, and 78 of the premating period (6%-7%; Table 1); days 0, 7, and 14 of the F_{1A} gestation (7%; Table 2); days 0, 4, and 7 of the F_{1A} lactation (5%-7%; Table 3); days 0, 7, 14, and 21 of the F_{1B} gestation (5%-6%); and day 0 of the F_{1B} lactation (5%). Weight gain at 700 ppm was 3%-12% lower than control during the premating and gestation periods and 19%-42% greater than control during the lactation periods.

In the F_1 generation at 700 ppm, male body weight was significantly lower than control on days 1, 8, 15, and 22 of the premating period (7%-8%; Table 1). Weight gain in all groups was comparable to control.

Among F_1 females, body weight was significantly lower (6%-9%) than control at 700 ppm during the entire premating period (Table 1) and F_{2A} and F_{2B} gestation periods (Table 2) and lactation periods (Table 3). Weight gain was 9%-12% lower than control during the premating and gestation periods and 38%-67% greater than control during the lactation periods.

Food consumption: No compound-related effects were observed in food efficiency (g/kg/day; data not shown). Decreased food consumption (g/animal/day) were noted at 700 ppm and followed a similar pattern as the decreased body weight discussed above (data not shown).

Compound intake: All values for mean compound intake were calculated by the reviewers using the summary group mean test article intake values.

In the F_0 generation, mean compound intake during premating was 8.1, 20.1, and 56.7 mg/kg/day for males and 8.8, 22.1, and 62.8 mg/kg/day for females at 100, 250, and 700 ppm, respectively. For females during F_{1A} gestation mean compound intake was 7.7, 19.0, and 53.3 mg/kg/day and during F_{1B} gestation it was 6.7, 17.0, and 46.0 mg/kg/day. During F_{1A} lactation mean compound intake was 14.3, 38.3, and 101.3 mg/kg/day and during F_{1B} lactation it was 14.0, 35.0, 95.7 mg/kg/day.

In the F_1 generation, mean compound intake during premating was 6.4, 16.5, and 47.3 mg/kg/day for males and 7.2, 18.9, and 52.3 mg/kg/day for females at 100, 250, and 700 ppm, respectively. For females during F_{2A} gestation mean compound intake was 7.0, 18.3, and 50.3 mg/kg/day and during F_{2B} gestation it was 6.7, 17.0, and 46.7 mg/kg/day. During F_{2A} lactation mean compound intake was 15.0, 34.0, and 100.0 mg/kg/day and during F_{2B} lactation it was 13.7, 33.3, and 98.3 mg/kg/day

Hematology: No compound-related effects were observed in any hematological parameter in F_1 males or females (data not shown). Incidental, but significant, findings consisted of the following:

Males	WBC	700 ppm	↑	p≤0.05
	EOSIN	250 ppm	↓	p≤0.05
	PT	100 ppm	↓	p≤0.01
Females	RETIC	700 ppm	↑	p≤0.05
	SEG	700 ppm	↓	p≤0.05
	LYMPH	700 ppm	↑	p≤0.05
	PTT	100 ppm	↑	p≤0.05

Clinical Chemistry: No compound-related effects were observed in any clinical chemistry parameters in F_1 males or females (data not shown). Incidental, but significant findings, consisted of the following:

Males	Creatinine	100 ppm	↑	p≤0.05
		700 ppm	↑	p≤0.05
	Chloride	700 ppm	↓	p≤0.05
	G-GLOB	700 ppm	↑	p≤0.01
	Cyt P-450	700 ppm	↑	p≤0.01
	N-Demethyl	700 ppm	↑	p≤0.05
	O-Demethyl	700 ppm	↑	p≤0.01
Females	Glucose	100 ppm	↑	p≤0.05
	GPT	250 ppm	↓	p≤0.01
	CK	100 ppm	↓	p≤0.05
		250 ppm	↓	p≤0.01
		700 ppm	↓	p≤0.05
	ALP	250 ppm	↓	p≤0.01
	Potassium	100 ppm	↑	p≤0.01
	G-GLOB	250 ppm	↑	p≤0.05
	N-Demethyl	250 ppm	↓	p≤0.01
	O-Demethyl	250 ppm	↑	p≤0.01
		700 ppm	↑	p≤0.01

The increased cytochrome P-450 content in males and demethylase activity in both sexes at 700 ppm are indicative of increased metabolism in the

liver in response to metabolism of a xenobiotic. This was considered to be an adaptive response rather than a toxicological response.

Gross pathology: No compound-related gross findings were observed in either sex or generation.

Organ weights: No compound-related effects in organ weights were observed in either sex or generation. Relative testes weight was significantly ($p \leq 0.05$) lower than control at 100 ppm in the F_1 generation. Since this finding was not seen in the previous generation or in either of the two highest dosage groups, it is considered to be incidental. Absolute ovarian weight was significantly ($p \leq 0.01$) lower than control at 700 ppm in the F_1 generation. Since a similar reduction was not seen in the previous generation or in relative ovarian weight and because there were no related histopathology findings, this observation is not considered to be compound-related.

Histopathology: No compound-related histopathological findings were observed in either sex or generation. Frequent findings in both the control and high dosage groups of both generations included clear and mononuclear cells in the liver, testicular atrophy, and decreased sperm in the epididymides.

Reproductive Toxicity

Compound-related reproductive effects were observed at 250 and 700 ppm as significantly decreased body weights among all pups in all litters. At 100 ppm, weight reductions were also noted occasionally. But they were less consistent and therefore considered to be biologically irrelevant. Summaries of these effects are presented in Tables 4-7. Detailed results are presented in the text below.

In the F_0 generation among F_{1A} pups (Table 4), mean pup body weight was significantly lower than control at 700 ppm on days 0-21 postpartum; at 250 ppm on day 0 postpartum; and at 100 ppm on day 21 postpartum. Among F_{1B} pups (Table 5), mean pup body weight was significantly lower than control at 700 ppm on days 0, 7, 14, and 21 postpartum; at 250 and 100 ppm on days 0-7 postpartum.

In the F_1 generation among F_{2A} pups (Table 6), mean pup body weight was significantly lower than control at 700 ppm on days 7-21 postpartum and at 250 ppm on day 7 postpartum. Among F_{2B} pups (Table 7), mean pup body weight was significantly lower than control at 700 ppm on days 1-21 postpartum, at 250 ppm on day 21 postpartum; and at 100 ppm on day 1 postpartum.

No compound-related clinical signs, external anomalies, or behavior abnormalities were observed in any litter or generation.

Study/Reporting Deficiencies

A protocol was not submitted. Results of the analysis for stability of the test material in the diet were not presented. However, since this information is available from other studies on NTN 33893 technical (see MRID# 422563-31 and 422563-32, which have study #s 100562 and 101931,

respectively), this deficiency will not alter the Core grading of this study.

D. REVIEWERS' DISCUSSION/CONCLUSIONS

Test Material Analyses: Concentration and homogeneity of the test material in the diet were confirmed to be overall within ±20% of nominal values. Results of the stability analysis were not presented.

Parental Toxicity: No parental toxicity was observed in this study. Body weights and food consumption were significantly decreased at 700 ppm in both sexes and generations. Food efficiency was not affected. The decreased food consumption was most likely due to non-palatability of the test compound which resulted in decreased body weight in both sexes and generations. No compound-related effects were seen in mortality, clinical signs, hematology parameters, organ weights, or gross or microscopic observations. Increased activity of selected liver enzymes was observed in both sexes at 700 ppm. In the absence of increase in liver-derived plasma enzymes, plasma bilirubin, liver triglycerides, changes in liver morphology, and organ weight, this was considered to be a physiological adaptation to the test compound rather than a toxicological response. Based on these results, the NOEL for parental toxicity was 700 ppm; the LOEL was not determined.

Reproductive Toxicity: Compound-related reproductive toxicity was observed at 250 and 700 ppm. It was manifested as decreased pup body weight. No compound-related effects were observed for any other reproductive parameter. Based on these results, the NOEL and LOEL for reproductive toxicity were 100 and 250 ppm, respectively.

E. CLASSIFICATION: CORE Minimum Data.

Parental toxicity NOEL = 700 ppm
Parental toxicity LOEL = Not determined

Reproductive toxicity NOEL = 100 ppm
Reproductive toxicity LOEL = 250 ppm (based on decreased pup body weight)

F. RISK ASSESSMENT: Not applicable

Table 1. Body Weight (g ± S.D.) During the Premating Period for Rats Fed Imidacloprid for Two Successive Generations[a]

Study Days	Dietary Level (ppm) 0	100	250	700
F_0 Males				
1	148 ± 9	146 ± 10	148 ± 11	147 ± 9
8	192 ± 12	188 ± 13	188 ± 15	182 ± 11*
29	292 ± 21	289 ± 22	283 ± 20	269 ± 25*
57	365 ± 28	367 ± 32	345 ± 43	335 ± 35*
84	396 ± 33	401 ± 36	382 ± 31	369 ± 37*
Wt. Gain 1-84[b]	248	255	234	222
F_0 Females				
1	112 ± 8	117 ± 8*	117 ± 6*	114 ± 8
8	135 ± 11	140 ± 8	140 ± 8	134 ± 8
29	185 ± 19	188 ± 11	188 ± 14	173 ± 13*
57	219 ± 26	221 ± 13	223 ± 20	206 ± 14*
84	230 ± 30	232 ± 14	236 ± 24	218 ± 14
Wt. Gain 1-84	118	115	119	104
F_1 Males				
1	251 ± 23	257 ± 22	242 ± 18	230 ± 26*
8	285 ± 25	293 ± 25	278 ± 21	265 ± 27*
29	352 ± 32	363 ± 33	344 ± 31	330 ± 34
57	404 ± 38	419 ± 41	396 ± 38	379 ± 43
85	433 ± 40	450 ± 45	426 ± 44	412 ± 49
105	449 ± 42	468 ± 48	445 ± 46	427 ± 48
Wt. Gain 1-105	198	211	203	197
F_1 Females				
1	179 ± 14	176 ± 14	175 ± 14	165 ± 16*
8	195 ± 15	192 ± 15	190 ± 15	178 ± 17*
29	225 ± 17	223 ± 19	218 ± 17	204 ± 20*
85	259 ± 20	256 ± 22	252 ± 18	235 ± 22*
57	245 ± 19	243 ± 20	240 ± 17	226 ± 22*
105	267 ± 21	263 ± 23	261 ± 19	244 ± 23*
Wt. Gain 1-105	88	87	86	79

[a]Data were extracted from Study No. 100647, pp. 89, 90, 93, 94, 125, 133, and 134.

[b]Standard deviation for weight gain was not provided.

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

Table 2. Body Weight (g ± S.D.) During Gestation for Rats Fed Imidacloprid for Two Successive Generations[a]

Study Days	Dietary Level (ppm) 0	100	250	700
F_0 Generation-F_{1A} litters				
0	230 ± 37	230 ± 15	235 ± 22	214 ± 17*
7	248 ± 36	246 ± 16	253 ± 24	231 ± 17*
14	274 ± 37	273 ± 17	282 ± 28	255 ± 19*
21	333 ± 43	332 ± 22	344 ± 32	314 ± 24
Wt. Gain 0-21[b]	103	102	109	100
F_0 Generation-F_{1B} litters				
0	254 ± 19	255 ± 13	257 ± 20	240 ± 18*
7	268 ± 21	269 ± 14	273 ± 20	255 ± 19*
14	294 ± 23	294 ± 15	298 ± 22	278 ± 21*
21	363 ± 34	364 ± 19	367 ± 30	342 ± 25*
Wt. Gain 0-21	109	109	110	102
F_1 Generation-F_{2A} litters				
0	260 ± 21	257 ± 21	261 ± 14	234 ± 23*
7	274 ± 22	268 ± 22	274 ± 16	246 ± 23*
14	295 ± 24	288 ± 22	294 ± 18	265 ± 24*
21	356 ± 31	350 ± 28	355 ± 26	321 ± 31*
Wt. Gain 0-21	96	93	94	87
F_1 Generation-F_{2B} litters				
0	279 ± 26	278 ± 28	272 ± 18	257 ± 22*
7	297 ± 29	293 ± 26	287 ± 20	271 ± 24*
14	322 ± 31	315 ± 27	309 ± 22	291 ± 27*
21	384 ± 41	374 ± 31	362 ± 30	349 ± 35*
Wt. Gain 0-21	105	96	90	92

[a]Data were extracted from Study No. 100647, pp. 127, 129, 130, 132, 135, 137, and 140.

[b]Standard deviation for weight gain was not provided.

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

Table 3. Body Weight (g ± S.D.) During Lactation for Rats Fed Imidacloprid for Two Successive Generations[a]

Study Days	Dietary Level (ppm) 0	100	250	700
F_0 Generation-F_{1A} litters				
0	247 ± 30	249 ± 15	253 ± 26	230 ± 18*
4	264 ± 29	262 ± 17	276 ± 25	245 ± 16*
7	273 ± 26	274 ± 18	288 ± 25	258 ± 17*
14	284 ± 30	285 ± 21	295 ± 22	270 ± 19
21	279 ± 30	278 ± 20	290 ± 23	268 ± 19
Wt. Gain 0-21[b]	32	29	37	38
F_0 Generation-F_{1B} litters				
0	274 ± 21	277 ± 21	281 ± 25	259 ± 19*
4	292 ± 23	293 ± 19	301 ± 23	281 ± 21
7	298 ± 22	301 ± 22	309 ± 25	288 ± 20
14	310 ± 25	313 ± 20	319 ± 22	297 ± 18
21	298 ± 23	300 ± 19	310 ± 20	293 ± 21
Wt. Gain 0-21	24	23	29	34
F_1 Generation-F_{2A} litters				
0	269 ± 26	258 ± 25	261 ± 19	239 ± 22*
4	283 ± 25	276 ± 25	280 ± 19	256 ± 22*
7	288 ± 25	283 ± 24	286 ± 19	263 ± 23*
14	302 ± 24	296 ± 24	299 ± 16	277 ± 19*
21	295 ± 22	292 ± 25	293 ± 18	275 ± 20*
Wt. Gain 0-21	26	34	32	36
F_1 Generation-F_{2B} litters				
0	294 ± 29	289 ± 28	284 ± 22	262 ± 23*
4	312 ± 29	308 ± 27	303 ± 23	286 ± 23*
7	318 ± 30	313 ± 27	312 ± 26	294 ± 27*
14	327 ± 29	324 ± 26	319 ± 24	302 ± 26*
21	315 ± 29	311 ± 24	308 ± 20	297 ± 22*
Wt. Gain 0-21	21	22	24	35

[a]Data were extracted from Study No. 100647, pp. 128, 129, 131, 132, 136, 137, 139, and 140.

[b]Standard deviation for weight gain was not provided.

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

Table 4. Effects of Dietary Administration of Imidacloprid on F_0 Reproductive Parameters, Offspring Survival, and F_{1A} Pup Body Weight[a]

Parameter	Dietary Level (ppm) 0	100	250	700
No. matings (F_0 parents)	29	28	30	30
Mating index (%)[b]	100	97	100	100
Fertility index (%)[c]	100	97	93	97
Gestation index (%)[d]	100	100	100	100
Gestation length (days)	22.2	22.1	22.3	22.1
No. females with liveborn pups	29	28	28	29
Total no. live pups				
Day 0	310	294	325	310
Day 4 precull	299	277	313	299
Day 21	207	206	214	203
Mean no. live pups/litter				
Day 0	10.7	10.5	11.6	10.7
Day 4 precull	10.3	9.9	11.2	10.3
Day 21	7.1	7.4	7.6	7.0
Live birth index (%)[e,h]	99	99	98	99
Viability index (%)[f,h]	96	94	96	96
Lactation index (%)[g,h]	92	94	96	89
Mean pup body weight (g)				
Day 0	5.5	5.6	5.6*	5.6*
Day 7	13.8	13.6	14.1	12.5*
Day 21	47.1	45.5*	46.4	40.8*
Sex ratio (% males day 0)	51	50	50	51

[a]Data were extracted from Study No. 100647, pp 161, 162, 171, 185, 193-200, 224, and 240

[b]Mating index: No. of mated females expressed as % of No. of paired females

[c]Fertility index: No. of pregnant females expressed as % of No. of paired females

[d]Gestation index: No. of females delivering a live litter expressed as % of No. of pregnant females

[e]Live birth index: Percentage of pups born alive based on No. of total pups born

[f]Viability index: Percentage of pups surviving four days based on No. of pups on day 1

[g]Lactation index: Percentage of pups surviving 21 days based on No. of pups on day 4 postcull

[h]Calculated by the reviewers; not statistically analyzed

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

Table 5. Effects of Dietary Administration of Imidacloprid on F_0 Reproductive Parameters, Offspring Survival, and F_{1B} Pup Body Weight[a]

Parameter	Dietary Level (ppm)			
	0	100	250	700
No. matings (F_0 parents)	29	29	30	30
Mating index (%)[b]	100	100	100	100
Fertility index (%)[c]	93	93	93	90
Gestation index (%)[d]	100	100	100	100
Gestation length (days)	22.0	22.1	22.1	22.1
No. females with liveborn pups	27	27	28	27
Total no. live pups				
Day 0	320	303	313	283
Day 4 precull	315	297	306	275
Day 21	199	212	214	193 (26)[e]
Mean no. live pups/litter				
Day 0	11.9	11.2	11.2	10.5
Day 4 precull	11.7	11.0	10.9	10.2
Day 21	7.4	7.9	7.6	7.4 (26)[e]
Live birth index (%)[f,i]	100	99	98	99
Viability index (%)[g,i]	98	98	98	97
Lactation index (%)[h,i]	95	99	97	90
Mean pup body weight (g)				
Day 0	5.6	5.8*	5.8*	5.8*
Day 7	14.6	15.2*	15.3*	14.0*
Day 21	49.8	50.2	49.7	45.0*
Sex ratio (% males day 0)	45	45	45	46

[a]Data were extracted from Study No. 100647, pp 163, 164, 174, 186, 201-208, 225, and 241

[b]Mating index: No. of mated females expressed as % of No. of paired females

[c]Fertility index: No. of pregnant females expressed as % of No. of paired females

[d]Gestation index: No. of females delivering a live litter expressed as % of No. of pregnant females

[e]No. of litters

[f]Live birth index: Percentage of pups born alive based on No. of total pups born

[g]Viability index: Percentage of pups surviving four days based on No. of pups on day 1

[h]Lactation index: Percentage of pups surviving 21 days based on No. of pups on day 4 postcull

[i]Calculated by the reviewers; not statistically analyzed

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

Table 6. Effects of Dietary Administration of Imidacloprid on F_1 Reproductive Parameters, Offspring Survival, and F_{2A} Pup Body Weight[a]

Parameter	Dietary Level (ppm)			
	0	100	250	700
No. matings (F_1 parents)	26	26	26	26
Mating index (%)[b]	100	100	100	100
Fertility index (%)[c]	85	89	85	96
Gestation index (%)[d]	100	100	100	100
Gestation length (days)	22.4	22.3	22.3	22.3
No. females with liveborn pups	22	23	21	25
Total no. live pups				
Day 0	222	254	197	239
Day 4 precull	202 (21)[e]	243	189	234
Day 21	148	172	141	177
Mean no. live pups/litter				
Day 0	10.1	11.0	9.4	9.6
Day 4 precull	9.6 (21)[e]	10.6	9.0	9.4
Day 21	7.0	7.5	6.7	7.1
Live birth index (%)[f,i]	97	99	98	100
Viability index (%)[g,i]	91	96	96	98
Lactation index (%)[h,i]	99	99	95	99
Mean pup body weight (g)				
Day 0	5.8	5.6	5.7	5.7
Day 7	15.0	14.9	14.4*	14.1*
Day 21	44.3	44.3	43.6	40.3*
Sex ratio (% males day 0)	51	53	46	48

[a]Data were extracted from Study No. 100647, pp 165, 166, 181, 187, 209-215, 226, and 242

[b]Mating index: No. of mated females expressed as % of total No. of paired females

[c]Fertility index: No. of pregnant females expressed as % of No. of paired females

[d]Gestation index: No. of females delivering a live litter expressed as % of No. of pregnant females

[e]No. of litters

[f]Live birth index: Percentage of pups born alive based on No. of total pups born

[g]Viability index: Percentage of pups surviving four days based on No. of pups on day 1

[h]Lactation index: Percentage of pups surviving 21 days based on No. of pups on day 4 postcull

[i]Calculated by the reviewers; not statistically analyzed

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

Table 7. Effects of Dietary Administration of Imidacloprid on F_1 Reproductive Parameters, Offspring Survival, and F_{2B} Pup Body Weight[a]

Parameter	Dietary Level (ppm)			
	0	100	250	700
No. matings (F_1 parents)	25	26	26	26
Mating index (%)[b]	96	100	100	100
Fertility index (%)[c]	92	77	100	100
Gestation index (%)[d]	100	100	100	100
Gestation length (days)	21.9	21.9	22.0	21.8
No. females with liveborn pups	24	20	26	26
Total no. live pups				
Day 0	260	202	229	278
Day 4 precull	254	198	222 (25)[e]	273
Day 21	180	146	172	185
Mean no. live pups/litter				
Day 0	10.8	10.1	9.2	10.7
Day 4 precull	10.6	9.9	8.9 (25)[e]	10.5
Day 21	7.5	7.3	6.9	7.1
Live birth index (%)[f,i]	98	99	97	99
Viability index (%)[g,i]	98	98	97	98
Lactation index (%)[h,i]	98	97	97	94
Mean pup body weight (g)				
Day 0	5.9	5.8	5.5	5.3
Day 7	15.6	15.5	15.1	14.2*
Day 21	50.7	50.5	48.7*	46.0*
Sex ratio (% males day 0)	48	52	46	50

[a]Data were extracted from Study No. 100647, pp 167, 168, 184, 188, 216-222, 227, and 243

[b]Mating index: No. of mated females expressed as % of total No. of paired females

[c]Fertility index: No. of pregnant females expressed as % of No. of paired females

[d]Gestation index: No. of females delivering a live litter expressed as % of No. of pregnant females

[e]No. litters

[f]Live birth index: Percentage of pups born alive based on No. of total pups born

[g]Viability index: Percentage of pups surviving four days based on No. of pups on day 1

[h]Lactation index: Percentage of pups surviving 21 days based on No. of pups on day 4 postcull

[i]Calculated by the reviewers; not statistically analyzed

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