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

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AUG 27 1992

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Iprodione - Two-Generation Reproduction Study in Rats

TO: Kathryn Davis/Barbara Briscoe PM 51
SRRD (H7508C)

FROM: K. Clark Swentzel *K. Clark Swentzel 8/18/92*
Toxicology Branch II
HED (H7509C)

THROUGH: Marcia van Gemert, Ph.D. *M van Gemert 8/23/92*
Branch Chief
Toxicology Branch II
HED (H7509C)

SUBMISSION:	S407869	**PROJECT NUMBER:**	2-0680
ID NUMBER:	109801-000264	**CASWELL NUMBER:**	470A
BARCODE:	D171983	**REGISTRANT:**	Rhone-Poulenc
CASE:	816345		

Requested Action

Review the attached 2-generation reproduction study.

Response

The subject study was reviewed by Clement Associates and the DER is attached.

Conclusions

Crl:CD rats received iprodione in the diet at concentrations of 0, 1000 or 2000/3000 ppm (dosages in males: 18.5, 61.4 and 154.8 mg/kg/day; in females: 22.49, 76.2, and 201.2 mg/kg/day, respectively). Parental toxicity was evident at 1000 ppm from decreased body weight, body weight gain and food consumption in both sexes. The NOEL and LOEL for parental toxicity were 300 and 1000 ppm, respectively.

Reproductive toxicity was evident at 2000/3000 ppm from decreased pup viability and body weight and an increased incidence in clinical signs in pups during the lactation period. The NOEL and LOEL for reproductive toxicity were 1000 and 2000 ppm, respectively.

Classification: Core-minimum. This study meets the minimum requirements for a two-generation reproduction study in rats (Guideline 83-4).

009695

DOC930144

FINAL

DATA EVALUATION REPORT

IPRODIONE

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, DPH	Date	8/13/92
Independent Reviewer	Sanju Diwan, Ph.D	Date	8/13/92
QA/QC Manager	Sharon Segal, Ph.D.	Date	8/13/92

Contract Number: 68D10075
Work Assignment Number: 1-98
Clement Number: 93-42
Project Officer: James Scott

Approved by: Clark Swentzel, Ph.D.
EPA Section Head, Review Section II
Toxicology Branch II/HED

Signature: K. Clark Swentzel

Date: 8/18/92

DATA EVALUATION REPORT

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STUDY TYPE: Reproductive toxicity

EPA IDENTIFICATION NUMBERS

TOX CHEM. NUMBER.:

MRID NUMBER.: 418716-01

009695

TEST MATERIAL: 3-(3,5-Dichlorophenyl)-N-isopropyl-2,4-dioxoimidazolidine-1-carboxamide

SYNONYMS: Iprodione; 26019RP; Glycophene; Kidan

SPONSOR: Rhone-Poulenc AG Company, Research Triangle Park, NC

STUDY NUMBER: HLA 6224-154

TESTING FACILITY: Hazleton Laboratories America, Inc., Madison, WI

TITLE OF REPORT: Two-Generation Reproduction Study with Iprodione Technical in Rats

AUTHOR: S.M. Henwood

REPORT ISSUED: April 29, 1991

CONCLUSIONS: In a two-generation reproduction study, Crl:CD®BR rats were fed iprodione in the diet at dosage levels of 0, 300, 1,000, or 2,000/3,000 ppm (for males 18.5, 61.4, and 154.8 mg/kg/day and for females 22.49, 76.2, and 201.2 mg/kg/day, respectively. Compound-related parental toxicity was observed at 1,000 and 2,000/3,000 ppm as evidenced by decreased body weight, body weight gain, and food consumption in both sexes and generations. The NOEL and LOEL for parental toxicity were 300 and 1,000 ppm, respectively.

Compound-related reproductive toxicity was observed at 2,000/3,000 ppm as evidenced by decreased pup viability and body weight and an increased incidence in clinical signs in pups during the lactation period. The NOEL and LOEL for reproductive toxicity were 1,000 and 2,000 ppm, respectively.

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.

A. MATERIALS

Test Compound

Purity:	96.2%
Description:	Cream-colored chunky powder
Lot number:	89062-01
Date Received:	July 13, 1989 and January 8, 1990
Contaminants:	Not reported

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

Test Animals

Species:	Rat
Strain:	Crl:CD®BR/VAF/PLUS
Source:	Charles River Laboratories, Portage, MI
Age:	F_0 males--66 days at start of study
	F_0 females--66 days at start of study
Weight:	F_0 males--267-360 g at start of study
	F_0 females--180-244 g at start of study

B. STUDY DESIGN

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

Mating: After 24 days of acclimatization followed by a minimum of 70 days of dietary treatment, the F_0 females were mated with males from the same group in a ratio of 1:1 until evidence of mating (vaginal plug or presence of sperm in a vaginal smear) was obtained or for a maximum of 21 days. The day on which mating was confirmed was designated day 0 of gestation. A 2-week rest period was allowed following weaning of the first litter and before mating for the second litter. The F_1 animals were mated twice in a similar fashion following 70 days on the test diet. Sibling matings were avoided.

Environmental conditions: A 12/12-hr light/dark cycle was maintained. The temperature was 72±3F°; the humidity was 50±20%.

Group arrangement: Parental animals were distributed amongst four groups using a computer-generated randomization based on body weight as follows:

009695

Test Group	Dietary Level (mg/kg/day)	Number Assigned per Group F_0 Males	F_0 Females	F_1 Males	F_1 Females
Control	0	28	28	28	28
Low dose	300	28	28	28	28
Mid dose	1,000	28	28	28	28
High dose	2,000* or 3,000	28	28	28	28

*F_1 pups from the 3,000 ppm group, selected as parental animals, received 3,000 ppm until mating for the F_2 generation. At that point, the dosage was reduced to 2,000 ppm owing to a significant decrease in body weight gain and decreased pup survival in the first generation.

Dosage administered: The test material was administered continuously in the diet (Purina® Certified Rodent Chow #5002) for two consecutive generations. Diets were prepared weekly and stored in a refrigerator until used. For each dosage level, a premix was prepared containing the appropriate amount of the test material and 100-200 g of Rodent Chow which was blended in a Waring blender. This mix was further diluted to achieve the appropriate concentration and blended for an additional 15 minutes. Stability of the test material in rodent chow at all dosage levels was analyzed after storage in a refrigerator for 2 days followed by storage at room temperature for 7 or 14 days and after storage in a freezer for 2 or 7 weeks. Homogeneity analyses of the test material in the diet at all dosage levels were conducted before the start of the study and once during the study. Concentration analyses were conducted weekly at all dosage levels for the first four weeks and monthly, thereafter, at alternating dosage levels.

No rationale for the selection of dosages was provided.

Observations: Observations for mortality, moribundity, and overt signs of toxicity were conducted twice a day. A more detailed clinical examination was performed weekly at the time of weighing. Food consumption for males was measured weekly throughout the study except during mating; for females it was measured weekly during premating (all females), days 0-4, 4-7, 7-14, and 14-20 during gestation (sperm-positive females), and days 0-4, 4-7, 7-10, 10-14, 14-16, 16-18, and 18-21 during lactation (females with litters). Body weight was recorded weekly for all males throughout the study except during mating; for females it was recorded weekly during the premating period (all females), on days 0, 7, 14, and 20 (sperm-positive females) during gestation, and on days 0, 4, 7, 14, and 21 (females with litters) during lactation. Terminal body weight data were recorded for all animals.

The following data were recorded for each litter:

- Number of live, dead, and stillborn pups, pup weight, and sex at birth

4

- Number of live pups, pup weight, external abnormalities, and sex on lactational days 0, 4, 7, 14, and 21

- Clinical signs

On lactational day 4, pups were randomly culled to 4/sex/litter whenever possible; culled pups were sacrificed, examined for visceral abnormalities and discarded. Pups found dead were examined externally and internally. Twenty eight male and twenty eight female F_1 pups were randomly selected as F_1 parental animals. Ten pups per sex, group, and generation were randomly selected for a complete necropsy.

Parental animals found dead or sacrificed moribund and females that did not deliver were necropsied. Following weaning, parental F_0 and F_1 animals were sacrificed and subjected to a gross pathological examination. The following tissues were preserved in 10% phosphate buffered formalin and examined histologically at the control and high-dosage levels with the exception of those designated with an asterisk (*):

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

<u>Statistical analysis</u>: The following analyses were conducted.

- Body weight, body weight change, food consumption, litter data, time to mate, and length of gestation--Levene's test of homogeneity of variances, ANOVA, and Dunnett's test for pairwise comparisons between groups (homogeneous data and transformed data)

- Reproduction indices--Fisher Irwin exact test and Cochran-Armitage trend test

- Pup body weight--ANCOVA with the number of live pups per litter as the covariate

<u>Compliance</u>:

- A signed Statement of No Data Confidentiality Claim, dated May 2, 1991, was provided.

- A signed Statement of Compliance with EPA and OECD GLPs, dated April 2 and May 2, 1991, was provided.

- A signed Quality Assurance Statement, dated April 29, 1991, was provided.

C. RESULTS

Test Material Analysis: Concentrations of the test material in the diets ranged from 96.5% to 112% of nominal values. Homogeneity analyses revealed concentrations from 89.3% to 109% of nominal values; stability analyses ranged from 93.0% (7 weeks frozen) to 99.9% (2 days refrigerated followed by 7 days at room temperature) of nominal values.

Parental Toxicity

Mortality: No compound-related mortalities were observed. Incidental deaths/moribund sacrifices are described below.

In the F_0 generation, two females (3,000 ppm) and two males (1,000 ppm) were sacrificed in moribund conditions. Clinical signs for the females included emaciation and hunched appearance. Clinical signs for the males included a swollen hindlimb in one animal and a broken nose in the other animal.

In the F_1 generation, one male (300 ppm) had a tissue mass and was sacrificed. Five females (one control; two at 300 ppm; one at 1,000 ppm, and one at 2,000/3,000 ppm) were found dead between gestation day 21 and lactation day 9 (second litter). The females did not exhibit any treatment-related clinical signs prior to death.

Clinical observations: No compound-related clinical signs were observed in any sex and generation.

Body weight: Compound-related effects in body weight and body weight gain were observed at 1,000 and 2,000/3,000 ppm. Summaries of body weight gain from selected time intervals are presented in Tables 1, 2, and 3. Detailed results are presented in the text.

In the F_0 generation, among males at 3,000 ppm, body weight (data not shown) decreased significantly by 15% during weeks 0-19 and 22% during the rest period between matings and until sacrifice. Body weight gain among males, decreased significantly at 3,000 ppm during weeks 0-19 by 45% and at 1,000 ppm during weeks 0-1 and 0-9 (data not shown) by 17%.

Among F_0 females during premating, body weight (data not shown) decreased significantly at 3,000 ppm starting week 1 by 12% and at 1,000 ppm starting week 2 by 6%. Body weight gain among females during premating, decreased significantly at 3,000 ppm during weeks 0-10 (Table 1) by 59% and at 1,000 ppm during weeks 0-10 by 22%. After the first mating, body weight at 3,000 ppm remained significantly decreased by 15%; at 1,000 ppm, it decreased significantly by 5% on gestation day 0 and lactation days 0 and 4. Body weight gain in the dams, decreased significantly at 3,000 ppm on gestation days 14-20 and 0-20 (23%, Table 2); it increased significantly at the same dosage level on lactation days 0-4, 14-21, and 0-21 (Table 3). After the second mating, body weight at 3,000 ppm still remained significantly decreased by 20%; at 1,000 ppm, it decreased significantly by 6% on gestation day 20. Body weight gain in the dams, decreased significantly at 3,000 ppm on gestation days 0-7, 14-20, and 0-20 (45%, Table 2) and at 1,000 ppm on gestation days 14-20 (20%, Table

6

2); it increased significantly at the same dosage level on lactation days 14-21 and 0-21 (Table 3).

In the F_1 generation, among males at 2,000/3,000 ppm, body weight (data not shown) decreased significantly by 25% during weeks 0-19 and 19% during the rest period between matings and until sacrifice. Body weight gain among males, decreased significantly at 2,000/3,000 ppm during weeks 0-19 by 17%.

Among F_1 females during premating, body weight decreased significantly at 2,000/3,000 ppm starting week 0 by 19% and at 1,000 ppm starting week 2 by 7%. Body weight gain among females during premating, decreased significantly at 2,000/3,000 ppm on weeks 4-10 (Table 1) by 14% and at 1,000 ppm on weeks 2-10 by 14% (data not shown). After the first mating, body weight at 2,000/3,000 ppm remained significantly decreased by 16%; at 1,000 ppm, it decreased significantly by 7% on gestation days, 7, 14, and 20 and lactation days 0, 4, and 7. Body weight gain in the dams, decreased significantly at 2,000/3,000 ppm on gestation days 14-20 and 0-20 (17%, Table 2); it increased significantly at the same dosage level on lactation days 14-21 and 0-21 and at 1,000 ppm on lactation days 0-21 (Table 3). After the second mating, body weight at 2,000/3,000 ppm remained significantly decreased by 15%; at 1,000 ppm, it decreased significantly by 7% on gestation days 0, 14, and 20 and lactation day 0. Body weight gain in the dams, decreased significantly at 2,000/3,000 ppm on gestation days 14-20 and 0-20 (26%, Table 2); it increased significantly at the same dosage level on lactation days 14-21 and 0-21 and at 1,000 ppm on lactation days 0-21 (Table 3).

Food consumption: Compound-related effects in food consumption data were observed at 1,000 and 2,000/3,000 ppm. Summaries of food consumption (g/animal/day) from selected time intervals are presented in Tables 4, 5, and 6. Detailed results are presented in the text. Food efficiency data were not submitted.

In the F_0 generation among males, food consumption decreased significantly at 3,000 ppm during the entire study and at 1,000 ppm during weeks 0-1, 7-8, 8-9, and 18-19. Among females during premating (Table 4), food consumption decreased significantly at 3,000 ppm during all weeks and at 1,000 ppm during weeks 0-1, 1-2, and 3-4. During the first gestation (Table 5), food consumption decreased significantly in the dams at 3,000 ppm on days 4-7 and 7-14. During the first lactation (Table 6), it decreased significantly at 3,000 ppm on days 10-14, 14-16, and 18-21. During the second gestation (Table 5), food consumption in the dams decreased significantly at 3,000 ppm on days 0-4, 4-7, and 14-20. During the second lactation (Table 6), it decreased significantly at 3,000 ppm on all days.

In the F_1 generation among males (Table 4), food consumption decreased significantly at 2,000/3,000 ppm during the entire study with a few exceptions. Among females during premating, food consumption decreased significantly at 2,000/3,000 ppm on weeks 1-4, 5-6, and 7-10 and at 1,000 ppm during weeks 1-4 and 9-10. During the first gestation (Table 5), food consumption decreased significantly in the dams at 2,000/3,000 ppm during days 4-7 and 7-14 and at 1,000 ppm on days 7-14. During the first lactation (Table 6), no differences were observed

7

between groups. During the second gestation (Table 5), food consumption in the dams decreased significantly at 2,000/3,000 ppm on days 14-20. During the second lactation (Table 6), it decreased significantly at 2,000/3,000 ppm on days 18-21.

Compound intake: In the F_0 generation, mean compound intake (corrected for purity) during the premating period was 16.5, 54.7, and 157.7 mg/kg/day for males and 21.2, 70.9, and 212.6 mg/kg/day for females at 300, 1,000, and 3,000 ppm, respectively. In the F_1 generation, mean compound intake during the premating period was 20.5, 68.1, and 151.9 mg/kg/day for males and 24.6, 81.5, and 189.7 mg/kg/day for females at 300, 1,000, and 2,000/3,000 ppm, respectively.

Gross and microscopic pathology: No compound-related gross or histologic findings were observed for any sex and generation.

Reproductive Toxicity: Compound-related reproductive effects were observed at 2,000/3,000 ppm. Summaries of these effects are presented in Tables 7-10. Detailed results are presented in the text.

In the F_0 generation, the number of live pups per litter decreased significantly at 3,000 ppm on day 0 among the first litters (Table 7) and on days 0 and 4 among the second litters (Table 8). The viability index decreased significantly at 300 and 3,000 ppm among the first litters. The viability and lactation indices decreased significantly at 3,000 ppm among the second litters. Pup male and female body weight decreased significantly at 3,000 ppm during the entire lactation among all litters. The decreased viability at 300 ppm was considered to be normal variation since no dose-related response was apparent and this effect was not observed among the second litters; other effects were considered to be treatment related.

In the F_1 generation, the duration of the first gestation (Table 9) was significantly shorter at 2,000/3,000 ppm than in the control group. Since this effect was not observed during the other gestations, it was not considered to be compound-related. The number of live pups/litter was significantly decreased at 2,000/3,000 ppm on day 0 among the first litters (Table 9) and on days 0 and 4 among the second litters (Table 10). The viability index at 1,000 and 2,000/3,000 ppm and the lactation index at 300 and 1,000 ppm, increased significantly among the first litters (Table 9). The viability index at 300 ppm decreased significantly among the second litters. These changes were effects of slightly decreased or increased viability in the control groups and were not treatment-related. Among all litters, total number of pups per litter delivered, decreased significantly at 2,000/3,000 ppm (data not shown). Among the first litters, pup male and female body weight decreased significantly at 2,000/3,000 ppm during the entire lactation (Table 9). Among the second litters, male pup body weight on lactation days 0, 4 (data not shown), and 21 and female pup body weight on lactation days 0, 14 (data not shown), and 21 decreased significantly. The decreased pup survival and pup body weight at 2,000/3,000 ppm were considered to be treatment-related effects.

Treatment-related clinical findings were observed at 2,000/3,000 ppm in all litters from both generations and included smallness of size, reduced mobility, unkempt appearance, hunching, or tremors. No compound-related gross malformations were noted in pups from any litter and generation.

D. REVIEWERS' DISCUSSION/CONCLUSIONS

Test Material Analyses: Concentration, stability and homogeneity of the test material in the diet were confirmed to be within ±12% of nominal concentrations.

Parental Toxicity: Compound-related toxicity was observed at 1,000 and 2,000/3,000 ppm in both sexes and generations. It was manifested as significantly decreased body weight, body weight gain, and food consumption. The effect on these parameters at 1,000 ppm were not as consistent and severe as those at 2,000/3,000 ppm. However, since they occurred in a dose-related pattern, they were considered to be treatment related. Mortality, clinical signs, and gross and microscopic findings were not affected by the test compound.

Based on these results, the parental toxicity NOEL and LOEL were 300 and 1,000 ppm, respectively.

Reproductive Toxicity: Compound-related reproductive toxicity was observed at 2,000/3,000 ppm. It was manifested in pups as significantly decreased viability and body weight and increased incidences of clinical signs across all litters and both sexes in both generations. Fertility, mating, and gestation indices and length of gestation were not affected by the test compound.

Based on these results the NOEL and LOEL for reproductive toxicity were 1,000 mg/kg/day and 2,000 ppm, respectively.

Reporting Deficiencies: Food efficiency was not reported.

E. CLASSIFICATION: CORE Minimum Data.

Parental toxicity NOEL = 300 ppm (approximately 21 mg/kg/day)
Parental toxicity LOEL = 1,000 ppm (approximately 69 mg/kg/day)

Reproductive toxicity NOEL = 1,000 ppm (approximately 69 mg/kg/day)
Reproductive toxicity LOEL = 2,000 ppm (approximately 178 mg/kg/day)

F. RISK ASSESSMENT: Not Applicable

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

Study Weeks	Dietary Level (ppm)			
	0	300	1,000	2,000/3,000[b]
F_0 Males				
0 - 1	28.4 ± 7.3	25.9 ± 6.6	22.1 ± 5.3**	9.3 ± 7.3**
0 - 4	107.6 ± 21.7	105.1 ± 18.0	99.7 ± 14.3	59.9 ± 23.9**
0 - 7	155.9 ± 31.3	149.3 ± 28.6	145.0 ± 20.0	74.5 ± 41.7**
0 - 10	188.3 ± 39.3	179.1 ± 35.1	169.1 ± 24.7	102.6 ± 36.3**
F_0 Females				
0 - 1	13.3 ± 8.9	10.3 ± 4.9	9.3 ± 5.1*	0.8 ± 5.7**
0 - 4	45.9 ± 9.9	42.6 ± 10.4	35.6 ± 8.9**	21.7 ± 8.4**
0 - 7	64.9 ± 11.5	62.4 ± 14.0	52.5 ± 11.6**	26.5 ± 11.7**
0 - 10	80.5 ± 14.8	77.8 ± 16.0	65.4 ± 12.2**	41.6 ± 12.2**
F_1 Males				
0 - 1	58.5 ± 5.2	57.7 ± 5.4	55.7 ± 6.9	40.7 ± 8.4**
0 - 4	179.4 ± 19.6	176.5 ± 15.9	176.7 ± 23.8	136.0 ± 25.9**
0 - 7	248.9 ± 33.8	253.3 ± 28.2	252.5 ± 32.3	205.0 ± 31.5**
0 - 10	295.2 ± 38.7	302.0 ± 35.3	301.2 ± 41.8	233.5 ± 33.5**
F_1 Females				
0 - 1	21.6 ± 6.8	19.8 ± 6.1	18.9 ± 5.3	22.8 ± 4.9
0 - 4	71.2 ± 10.0	65.6 ± 14.2	58.9 ± 10.3**	61.6 ± 11.2**
0 - 7	99.0 ± 17.9	93.8 ± 17.8	85.2 ± 14.2**	85.3 ± 14.5**
0 - 10	116.5 ± 20.2	108.2 ± 20.9	100.0 ± 16.5**	98.4 ± 15.9**

[a]Data were extracted from Study No. HLA 6224-154, Tables 29 and 35.

[b]For the F_0 generation, 3,000 ppm; for the F_1 generation, 2,000 ppm

*Significantly different from control (p≤0.05)

**Significantly different from control (p≤0.01)

009695

Table 2. Mean Body Weight Gain (g ± S.D.) During Gestation for Dams Fed Iprodione for Two Successive Generations[a]

Gestational Days:	Dietary Level (ppm) 0	300	1,000	2,000/3,000[b]
F_0 Generation - F_{1A} Litters				
0 - 7	22.3 ± 8.2	26.6 ± 7.3	29.8 ± 8.0**	21.6 ± 7.1
7 - 14	20.9 ± 8.3	20.1 ± 6.9	19.4 ± 13.8	18.2 ± 6.4
14 - 20	65.1 ± 13.4	63.1 ± 12.9	58.0 ± 21.8	47.4 ± 13.5**
0 - 20	108.3 ± 16.7	109.8 ± 16.0	107.2 ± 30.7	87.2 ± 16.0**
F_0 Generation - F_{1B} Litters				
0 - 7	31.0 ± 9.0	33.7 ± 8.6	32.2 ± 9.9	22.2 ± 7.8**
7 - 14	17.1 ± 9.3	20.4 ± 7.1	18.8 ± 4.0	15.2 ± 9.4
14 - 20	71.1 ± 13.6	68.9 ± 14.7	57.0 ± 18.0**	26.9 ± 21.6**
0 - 20	118.9 ± 18.8	123.0 ± 20.4	108.0 ± 17.7	64.4 ± 26.4**
F_1 Generation - F_{2A} Litters				
0 - 7	28.3 ± 9.6	32.0 ± 9.2	28.3 ± 7.4	25.7 ± 7.0
7 - 14	30.7 ± 10.2	28.5 ± 7.7	28.9 ± 6.9	28.8 ± 6.3
14 - 20	64.4 ± 11.5	60.4 ± 21.5	63.8 ± 10.6	51.5 ± 8.8**
0 - 20	123.4 ± 15.4	120.9 ± 23.5	121.0 ± 14.3	106.0 ± 12.7**
F_1 Generation - F_{2B} Litters				
0 - 7	29.5 ± 8.4	30.1 ± 10.3	29.7 ± 7.2	26.3 ± 7.9
7 - 14	23.9 ± 12.2	25.6 ± 7.1	23.7 ± 5.1	22.6 ± 5.9
14 - 20	69.5 ± 18.7	66.7 ± 15.0	61.5 ± 10.7	47.7 ± 12.9**
0 - 20	123.0 ± 23.9	122.3 ± 19.2	115.0 ± 9.8	96.7 ± 22.1**

[a]Data were extracted from Study No. HLA 6224-154, Tables 30, 33, 36, and 39.

[b]For the F_0 generation, 3,000 ppm; for the F_1 generation, 2,000 ppm

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

11

Table 3. Mean Body Weight Gain (g ± S.D.) During Lactation for Dams Fed Iprodione for Two Successive Generations[a]

Lactational Days:	Dietary Level (ppm)			
	0	300	1,000	2,000/3,000[b]
F_0 Generation - F_{1A} Litters				
0 - 4	0.9 ± 10.7	1.0 ± 10.3	7.3 ± 16.5	10.3 ± 16.6*
4 - 7	5.7 ± 7.6	6.7 ± 12.3	8.4 ± 7.8	2.9 ± 7.8
14 - 21	-14.3 ± 11.1	-17.5 ± 12.7	-13.3 ± 16.5	-3.7 ± 13.2*
0 - 21	0.1 ± 14.4	-2.0 ± 14.7	11.7 ± 26.5	14.1 ± 20.3*
F_0 Generation - F_{1B} Litters				
0 - 4	7.2 ± 14.7	7.4 ± 10.0	11.7 ± 13.0	8.5 ± 16.4
4 - 7	2.7 ± 10.2	1.3 ± 11.0	6.1 ± 13.8	7.5 ± 12.3
14 - 21	-17.2 ± 13.1	-18.3 ± 13.7	-18.1 ± 15.3	6.8 ± 13.1**
0 - 21	-0.4 ± 17.4	-4.6 ± 14.6	8.0 ± 25.9	35.9 ± 22.1**
F_1 Generation - F_{2A} Litters				
0 - 4	14.0 ± 10.4	14.1 ± 8.9	18.5 ± 11.0	14.6 ± 9.8
4 - 7	4.6 ± 6.3	4.3 ± 7.6	8.3 ± 7.7	6.4 ± 8.0
14 - 21	-19.9 ± 15.8	-24.8 ± 11.7	-15.5 ± 12.5	-7.6 ± 13.6**
0 - 21	3.7 ± 22.1	2.9 ± 19.3	21.5 ± 13.5**	24.6 ± 13.1**
F_1 Generation - F_{2B} Litters				
0 - 4	9.7 ± 14.7	1.4 ± 28.0	17.9 ± 14.1	7.9 ± 20.7
4 - 7	-0.3 ± 9.5	5.4 ± 12.4	4.5 ± 5.6	5.2 ± 13.0
14 - 21	-24.2 ± 15.0	-22.2 ± 14.7	-18.6 ± 11.7	-7.7 ± 15.3**
0 - 21	-7.3 ± 26.0	-6.7 ± 32.5	12.0 ± 18.3*	22.8 ± 19.1**

[a]Data were extracted from Study No. HLA 6224-154, Tables 31, 34, 37, and 40.

[b]For the F_0 generation, 3,000 ppm; for the F_1 generation, 2,000 ppm

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

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

Table 4. Mean Food Consumption (g/day ± S.D.) During the Premating Period for Rats Fed Iprodione for Two Successive Generations[a]

Study Weeks	Dietary Level (ppm)			
	0	300	1,000	2,000/3,000[b]
F_0 Males				
0 - 1	22.7 ± 2.2	21.8 ± 1.8	21.0 ± 1.7**	19.1 ± 1.9**
3 - 4	25.0 ± 3.1	24.4 ± 2.1	24.2 ± 2.3	21.4 ± 3.1**
6 - 7	25.2 ± 2.9	24.6 ± 2.1	23.8 ± 1.9	20.0 ± 4.3**
9 - 10	25.8 ± 2.7	25.4 ± 2.5	25.1 ± 2.1	22.5 ± 2.4**
F_0 Females				
0 - 1	18.5 ± 2.5	17.5 ± 1.8	16.3 ± 1.4**	14.5 ± 2.1**
3 - 4	19.3 ± 2.2	18.7 ± 2.0	17.8 ± 2.0*	17.4 ± 1.9**
6 - 7	18.0 ± 2.8	18.0 ± 2.3	17.3 ± 1.3	16.2 ± 1.3**
9 - 10	19.3 ± 2.1	18.9 ± 2.1	18.0 ± 1.8	17.6 ± 1.7*
F_1 Males				
0 - 1	28.1 ± 2.0	27.6 ± 2.2	26.9 ± 2.5	20.7 ± 2.9**
3 - 4	29.6 ± 2.7	28.9 ± 2.2	28.5 ± 3.1	23.6 ± 3.8**
6 - 7	28.0 ± 3.9	29.1 ± 2.3	28.2 ± 2.7	23.7 ± 3.3**
9 - 10	28.3 ± 2.1	28.6 ± 2.3	28.0 ± 2.5	23.7 ± 3.3**
F_1 Females				
0 - 1	20.0 ± 2.2	19.4 ± 1.9	18.8 ± 2.7	18.5 ± 2.8
3 - 4	20.2 ± 1.9	20.1 ± 2.1	17.8 ± 1.8**	18.2 ± 4.6*
6 - 7	19.2 ± 2.7	19.2 ± 2.4	18.4 ± 2.1	20.7 ± 16.1
9 - 10	19.8 ± 1.8	19.0 ± 3.2	17.5 ± 1.6**	16.8 ± 1.9**

[a]Data were extracted from Study No. HLA 6224-154, Tables 41 and 47.

[b]For the F_0 generation, 3,000 ppm; for the F_1 generation, 2,000 ppm

*Significantly different from control (p≤0.05)

**Significantly different from control (p≤0.01)

Table 5. Mean Food Consumption (g/day ± S.D.) During Gestation for Rats Fed Iprodione for Two Successive Generations[a]

Gestational Days:	Dietary Level (ppm) 0	300	1,000	2,000/3,000[b]
F_0 Generation - F_{1A} Litters				
0 - 4	21.4 ± 2.9	21.9 ± 2.9	21.0 ± 5.3	20.2 ± 2.3
4 - 7	23.1 ± 2.8	24.0 ± 2.4	24.6 ± 5.5	20.2 ± 4.9*
7 - 14	22.8 ± 1.9	22.0 ± 2.1	22.0 ± 3.2	19.5 ± 2.7**
14 - 20	20.9 ± 1.9	20.4 ± 2.9	19.4 ± 5.3	18.6 ± 3.0
F_0 Generation - F_{1B} Litters				
0 - 4	25.9 ± 2.6	25.7 ± 3.5	24.4 ± 3.3	21.7 ± 2.9**
4 - 7	27.2 ± 2.6	26.2 ± 4.1	25.6 ± 3.5	21.2 ± 2.6**
7 - 14	25.5 ± 2.4	26.3 ± 3.6	24.6 ± 3.8	23.4 ± 4.0
14 - 20	23.0 ± 2.1	23.1 ± 2.6	22.6 ± 3.2	20.0 ± 5.0*
F_1 Generation - F_{2A} Litters				
0 - 4	22.6 ± 2.9	22.6 ± 3.0	21.4 ± 2.6	20.6 ± 3.2
4 - 7	24.3 ± 3.5	24.7 ± 3.3	23.0 ± 2.5	20.9 ± 2.4**
7 - 14	24.7 ± 3.5	24.2 ± 2.8	22.5 ± 2.2*	21.2 ± 2.6**
14 - 20	21.4 ± 2.7	20.9 ± 1.9	20.7 ± 2.7	19.9 ± 2.9
F_1 Generation - F_{2B} Litters				
0 - 4	22.9 ± 3.3	22.7 ± 3.2	22.5 ± 2.1	20.9 ± 2.7
4 - 7	24.5 ± 3.8	24.8 ± 3.7	23.4 ± 2.0	22.0 ± 3.3
7 - 14	24.6 ± 3.5	24.8 ± 3.5	23.3 ± 2.2	22.7 ± 3.3
14 - 20	20.8 ± 4.0	20.5 ± 2.1	18.8 ± 2.6	17.5 ± 2.5**

[a]Data were extracted from Study No. HLA 6224-154, Tables 42, 45, 48, and 51.

[b]For the F_0 generation, 3,000 ppm; for the F_1 generation, 2,000 ppm

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

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

Table 6. Mean Food Consumption (g/day ± S.D.) During Lactation for Rats Fed Iprodione for Two Successive Generations[a]

Lactational Days:	Dietary Level (ppm) 0	300	1,000	2,000/3,000[b]
F_0 Generation - F_{1A} Litters				
0 - 4	21.6 ± 6.0	26.2 ± 4.8	25.4 ± 4.8	23.8 ± 7.5
4 - 7	38.3 ± 4.4	39.3 ± 5.1	36.6 ± 8.6	34.2 ± 11.0
14 - 16	59.5 ± 6.0	60.4 ± 4.1	55.9 ± 12.3	50.0 ± 12.7**
18 - 21	68.1 ± 10.2	72.3 ± 6.6	60.4 ± 22.9	57.2 ± 8.5**
F_0 Generation - F_{1B} Litters				
0 - 4	28.6 ± 6.9	29.1 ± 4.8	26.6 ± 8.2	20.2 ± 9.1**
4 - 7	39.2 ± 5.3	39.9 ± 5.1	38.5 ± 7.6	31.5 ± 8.7**
14 - 16	62.6 ± 4.7	59.8 ± 10.0	59.2 ± 13.3	46.8 ± 15.1**
18 - 21	69.1 ± 19.5	72.9 ± 8.8	67.7 ± 13.5	48.1 ± 19.5**
F_1 Generation - F_{2A} Litters				
0 - 4	30.7 ± 5.7	29.8 ± 5.4	29.9 ± 3.4	27.5 ± 3.7
4 - 7	37.4 ± 4.5	37.6 ± 5.2	38.3 ± 4.1	37.3 ± 5.3
14 - 16	59.3 ± 4.4	58.8 ± 11.8	64.6 ± 17.8	57.4 ± 8.5
18 - 21	66.8 ± 14.6	67.3 ± 15.1	67.9 ± 5.1	56.7 ± 16.0
F_1 Generation - F_{2B} Litters				
0 - 4	29.0 ± 4.4	25.9 ± 8.7	28.1 ± 6.5	22.9 ± 10.1
4 - 7	37.1 ± 7.0	36.2 ± 8.8	38.6 ± 6.6	35.5 ± 11.9
14 - 16	57.5 ± 11.6	58.2 ± 4.8	57.5 ± 12.7	54.7 ± 14.2
18 - 21	69.6 ± 5.9	65.9 ± 19.7	68.8 ± 17.4	51.6 ± 18.8*

[a]Data were extracted from Study No. HLA 6224-154, Tables 43, 46, 49, and 52.

[b]For the F_0 generation, 3,000 ppm; for the F_1 generation, 2,000 ppm

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

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

Table 7. Summary of Effects of Dietary Administration of Iprodione on F_{1A} Reproductive Parameters, Offspring Survival, and Pup Body Weight[a]

Parameter	Dietary Level (ppm) 0	300	1,000	3,000
No. matings (F_0 parents)	28	28	28	28
Mating index (%)[b]	100	100	100	100
Fertility index-female (%)[c]	96	89	96	100
Fertility index-male (%)	96	89	96	100
Gestation index (%)[d]	100	100	93	100
Gestation length (days)	21.8	22.0	22.2	22.0
No. females with liveborn pups	27	25	25	28
Total no. stillborn pups	7	5	12	18
Total no. stillborn, uncertain	1	0	15	3
Total no. live pups				
Day 0	369	324	342	337
Day 4 precull	366	314	336	324
Day 21	214	198	199	207
Mean no. live pups/litter				
Day 0	13.7	13.0	13.7	12.0*
Day 4 precull	13.6	12.6	13.4	12.5 (26)[e]
Day 21	7.9	7.9	7.9	7.9
Live birth index (%)[f]	98	99	91	94
Viability index (%)[g]	99	97*	98	96**
Lactation index (%)[h]	100	99	100	100
Mean pup body weight (g)[i]				
Day 0, males	6.3	6.4	6.2	5.6**
females	5.9	6.0	5.9	5.3**
Day 7, males	15.9	16.8	16.0	13.2**
females	15.1	16.0	15.3	12.6**
Day 21, males	53.3	56.4	53.2	35.3**
females	51.2	53.5	50.7	33.8**
Sex ratio (% male day 0)	50	51	49	56

[a]Data were extracted from Study No. HLA 6224-154, Tables 55 and 57.

[b]Mating index: No. sperm-positive females expressed as % of total no. mated females

[c]Fertility index: No. females delivering a litter expressed as % of no. sperm-positive females

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

[e]Number of litters reduced owing to total litter mortality

[f]Live birth index: Percentage of pups surviving one day (based on mean no. of pups per litter)

[g]Viability index: Percentage of pups surviving four days (based on total no. of live pups per group)

[h]Lactation index: Percentage of pups surviving 21 days based on No. pups on day 4 postcull (based on total no. of live pups per group)

[i]Covariate adjusted body weights

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

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

16

Table 8. Summary of Effects of Dietary Administration of Iprodione on F_{1B} Reproductive Parameters, Offspring Survival, and Pup Body Weight[a]

Parameter	Dietary Level (ppm) 0	300	1,000	3,000
No. matings (F_0 parents)	28	28	28	28
Mating index (%)[b]	96	100	93	96
Fertility index-female (%)[c]	96	86	96	88
Fertility index-male (%)	93	86	93	85
Gestation index (%)[d]	100	100	100	87
Gestation length (days)	22.1	22.3	22.2	22.4
No. females with liveborn pups	26	24	25	20
Total no. stillborn pups	14	12	4	33
Total no. stillborn, uncertain	2	0	1	0
Total no. live pups				
Day 0	355	324	305	187
Day 4 precull	347	320	295	148
Day 21	195	186	182	79
Mean no. live pups/litter				
Day 0	13.7	13.5	12.2	9.4**
Day 4 precull	13.4	13.3	11.8	8.7** (17)[e]
Day 21	7.8 (25)[e]	7.8	7.3	6.6 (12)[e]
Live birth index (%)[f]	96	96	99	85
Viability index (%)[g]	98	99	97	79**
Lactation index (%)[h]	98	100	99	67**
Mean pup body weight (g)[i]				
Day 0, males	6.4	6.6	6.3	5.0**
females	6.0	6.2	5.9	4.7**
Day 7, males	17.0	18.3	16.8	11.2**
females	16.3	17.3	15.7	11.1**
Day 21, males	57.4	60.9	56.1	33.6**
females	54.6	58.1	52.2	35.3**
Sex ratio (% male day 0)	48	46	55	47

[a]Data were extracted from Study No. HLA 6224-154, Tables 56 and 58.

[b]Mating index: No. sperm-positive females expressed as % of total no. mated females

[c]Fertility index: No. females delivering a litter expressed as % of no. sperm-positive females

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

[e]Number of litters reduced owing to total litter mortality

[f]Live birth index: Percentage of pups surviving one day (based on mean no. of pups per litter)

[g]Viability index: Percentage of pups surviving four days (based on total no. of live pups per group)

[h]Lactation index: Percentage of pups surviving 21 days based on No. pups on day 4 postcull (based on total no. of live pups per group)

[i]Covariate adjusted body weights

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

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

Parameter	Dietary Level (ppm) 0	300	1,000	2,000 or 3,000
No. matings (F_1 parents)	28	28	28	28
Mating index (%)[b]	93	100	96	96
Fertility index-female (%)[c]	92	89	96	89
Fertility index-male (%)	86	89	93	86
Gestation index (%)[d]	100	96	100	100
Gestation length (days)	22.4	22.6	22.2	22.1*
No. females with liveborn pups	24	24	26	24
Total no. stillborn pups	5	9	2	4
Total no. stillborn, uncertain	0	0	0	0
Total no. live pups				
Day 0	341	322	368	286
Day 4 precull	319	311	361	279
Day 21	183	187	208	181
Mean no. live pups/litter				
Day 0	14.2	13.4	14.2	11.9**
Day 4 precull	13.3	13.0	13.9	11.6
Day 21	7.9 (23)[e]	7.8	8.0	7.9 (23)[e]
Live birth index (%)[f]	99	97	100	99
Viability index (%)[g]	94	97	98**	98*
Lactation index (%)[h]	96	100**	100**	95
Mean pup body weight (g)[i]				
Day 0, males	6.4	6.5	6.1	5.8**
females	6.0	6.0	5.8	5.5**
Day 7, males	16.8	17.2	16.0	15.7*
females	15.8	16.1	14.8	14.9
Day 21, males	55.6	58.0	53.2	43.1**
females	53.0	54.7	50.2	42.1**
Sex ratio (% male day 0)	48	49	55	50

[a]Data were extracted from Study No. HLA 6224-154, Tables 61 and 63.

[b]Mating index: No. sperm-positive females expressed as % of total no. mated females

[c]Fertility index: No. females delivering a litter expressed as % of no. sperm-positive females

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

[e]Number of litters reduced owing to total litter mortality

[f]Live birth index: Percentage of pups surviving one day (based on mean no. of pups per litter)

[g]Viability index: Percentage of pups surviving four days (based on total no. of live pups per group)

[h]Lactation index: Percentage of pups surviving 21 days based on No. pups on day 4 postcull (based on total no. of live pups per group)

[i]Covariate adjusted body weights

*Significantly different from control (p≤0.05)

**Significantly different from control (p≤0.01)

14

Table 10. Summary of Effects of Dietary Administration of Iprodione on F_{2B} Reproductive Parameters, Offspring Survival, and Pup Body Weight[a]

Parameter	Dietary Level (ppm) 0	300	1,000	2,000 or 3,000
No. matings (F_1 parents)	28	28	28	28
Mating index (%)[b]	100	100	100	93
Fertility index-female (%)[c]	75	79	86	84
Fertility index-male (%)	75	79	86	75
Gestation index (%)[d]	95	100	100	95
Gestation length (days)	22.2	22.5	22.4	22.1
No. females with liveborn pups	19	21	23	20
Total no. stillborn pups	13	4	17	24
Total no. stillborn, uncertain	3	0	0	1
Total no. live pups				
Day 0	277	277	313	234
Day 4 precull	273	257	308	226
Day 21	152	152	175	142
Mean no. live pups/litter				
Day 0	14.6	13.2	13.6	11.7*
Day 4 precull	14.4	12.2	14.0 (22)[e]	11.3**
Day 21	8.0	8.0	7.9	7.5 (19)[e]
Live birth index (%)[f]	92	97	95	91
Viability index (%)[g]	99	93*[g]	98	97
Lactation index (%)[h]	100	95	99	97
Mean pup body weight (g)[i]				
Day 0, males	6.4	6.3	6.2	5.7**
females	5.9	5.9	5.9	5.4*
Day 7, males	16.2	17.4	16.5	14.9
females	15.5	16.3	15.5	14.3
Day 21, males	54.2	59.1	55.0	43.4**
females	51.2	55.4	51.7	41.7**
Sex ratio (% male day 0)	48	49	48	46

[a]Data were extracted from Study No. HLA 6224-154, Tables 62 and 64.

[b]Mating index: No. sperm-positive females expressed as % of total no. mated females

[c]Fertility index: No. females delivering a litter expressed as % of no. sperm-positive females

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

[e]Number of litters reduced owing to total litter mortality

[f]Live birth index: Percentage of pups surviving one day (based on mean no. of pups per litter)

[g]Viability index: Percentage of pups surviving four days (based on total no. of live pups per group)

[h]Lactation index: Percentage of pups surviving 21 days based on No. pups on day 4 postcull (based on total no. of live pups per group)

[i]Covariate adjusted body weights

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

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