Incorfile

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

010570

SEP 14 1993

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Iprodione- Combined chronic toxicity/carcinogenicity in rats
6(a)(2) data

TO: Barbara Briscoe PM 51
Special Review and Reregistration Division

FROM: K. Clark Swentzel, Section Head K. Clark Swentzel 9/9/93
Toxicology Branch II

THROUGH: Marcia van Gemert, Ph.D. Marcia van Gemert 9/10/93
Branch Chief
Toxicology Branch II

Submission: S435926
Barcode: D188475
MRID NO.: 426378-01
CASWELL NO.: 470A
PC CODE: 109801
REGISTRANT: Rhone-Poulenc

Action Requested

120 day review

Response

This study has been reviewed by Clement; the DER is attached.

Conclusions

Iprodione was fed to male and female Sprague-Dawley rats at dietary levels of 0, 150, 300 or 1600 ppm (6.1, 12.4, 69.0 mg/kg/day in males and 8.4, 16.5, 95.0 mg/kg/day in females) for 2 years.

At 1600 ppm, an increased incidence of benign interstitial cell tumors of the testes was observed. No increase in the incidence of any tumor type was observed in treated females in this study.

At 300 ppm, generalized enlargement of the cells of the zona glomerulosa in males and females and rarefaction and fine vacuolation of the zona fasciculata in the adrenal cortex were observed in males. Generalized fine vacuolation of the zona reticularis in the adrenal cortex was also seen in males. Also, males showed interstitial cell hyperplasia in the testes, reduced spermatozoa in the epididymides, reduced secretion of the seminal vesicles and an increased liver weight (adjusted for body weight). Increased hemosiderosis in spleen was noted in females. Males showed centrilobular hepatocellular enlargement at the interim sacrifice.

At 1600 ppm, decreases were observed in body weight gain (≈14-74%) and food consumption (≈5-8%) among males and females. At necropsy, males showed increases in testes (with epididymides) weights (after adjustment for body weight), testicular masses, small prostates and small seminal vesicles with minimal contents. Histopathology revealed atrophy of the prostate and seminiferous tubule, prominent abnormal spermatogenic cells and centrilobular hepatocellular enlargement in males. The effects in the adrenal cortex noted at 300 ppm were also observed in males at this dietary level. At the interim sacrifice both sexes showed generalized rarefaction and fine vacuolation of the zona fasiculata, males showed generalized enlargement of the cells of the zona glomerulosa and generalized fine vacuolation of the zona reticularis of the adrenal cortex and females showed increased extramedullary hematopoiesis in the spleen.

NOEL: 150 ppm (6.1 & 8.4 mg/kg/day in males and females, respectively)

LEL: 300 ppm (12.4 & 16.5 mg/kg/day in males and females, respectively)

Core Classification

The contract reviewer classified this study Core Supplementary for a combined chronic toxicity/carcinogenicity study since it was concluded that a NOEL for systemic toxicity was not established. The registrant was subsequently asked by TB II (via telephone) to provide historical control data regarding the spontaneous incidence of fine vacuolation of the zona reticularis of the adrenal cortex in Sprague-Dawley males from the testing facility. Following this request, slides prepared from the adrenals of 350 control males from 7 studies were reexamined for this lesion. These data have been received and show that the incidence of this lesion in low-dose males was comparable to the mean (approximately 23%) from the historical control data (attachment 1) which were generated between February 1988 and June 1989 (attachment 2); the subject study was initiated in 1990. The concurrent control data appeared to be atypical. Based on the assessment of the submitted historical control data, it is TB II's opinion that the classification of chronic toxicity segment of this study should be Core-minimum. The Core Classification of the carcinogenicity segment of this study will be determined following review by the HED Cancer Peer Review Committee. This study will be considered concurrently with

a carcinogenicity study in mice (currently under review in TB II) as well as a Discussion Document (Iprodione: Carcinogenicity in Rodents MRID No. 428250-01) submitted by the registrant which includes a discussion of the possible mechanisms of action for the tumors induced in these studies (attachment 3).

Pending regulatory actions

A preliminary report from a mouse carcinogenicity study, dated March 15, 1993, was previously submitted under 6(a)(2) to the Agency. The report indicated that "there appears to be an increased incidence of benign and malignant liver tumors in both sexes along with an increased incidence of benign ovarian tumors at or above the maximum tolerated dose (4000 ppm)." As noted above, the final report for this study is currently under review in TB II.

Due to the many food uses for Iprodione, both of these studies were given high priority for scientific review and probable cancer peer review. Since a consensus on the possible cancer risk for the consuming public can not be attained until these reviews have been completed, pending regulatory actions involving Iprodione can not be toxicologically supported at this time.

010570

FINAL

DATA EVALUATION REPORT

Iprodione

Study Type:
Combined Chronic Toxicity/Carcinogenicity in Rats

Study Title:
Iprodione: Potential Tumorigenic and Toxic Effects in Prolonged Dietary Administration to Rats

Prepared for:

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 22031-1207

June 15, 1993

Principal Reviewer: Carrie Rabe, Ph.D. — Date: 6/14/93

Independent Reviewer: John Liccione, Ph.D. — Date: 6/14/93

QA/QC Manager: Sharon Segal, Ph.D. — Date: 6/14/93

Contract Number: 68D10075
Work Assignment Number: 2-89
Clement Number: 228
Project Officer: Caroline Gordon

EPA Reviewer and Section Head:
Clark Swentzel, Review Section II,
Toxicology Branch II, Health Effects Division

Signature: C. Swentzel
Date: 6/24/93

DATA EVALUATION REPORT

STUDY TYPE: Combined chronic toxicity/carcinogenicity in rats

TEST MATERIAL: Iprodione

P.C. NO.: 109801

TOX CHEMICAL NO.: 470A

SYNONYM: 26019 RP; Rovral®

MRID Number: 426378-01

STUDY NUMBER: RNP 346/920808

SPONSOR: Rhone Poulenc Agrochimie
Department de Toxicologie
14-20 rue Pierre Baizet,
BP 9163, 69293 Lyon Cedex 09, France

TESTING FACILITY: Department of Rodent Toxicology
Huntingdon Research Centre, Ltd.
P.O. Box 2
Huntingdon Cambridgeshire
PE18 6ES, England

TITLE OF REPORT: Iprodione: Potential Tumorigenic and Toxic Effects in Prolonged Dietary Administration to Rats

AUTHORS: P.R. Chambers, D. Crook, W.A. Gibson, C. Gopinath, S.A. Ames

REPORT ISSUED: December 15, 1992

QUALITY ASSURANCE: A signed quality assurance statement, dated December 15, 1992, was provided. A GLP certification statement and a flagging statement were present.

CONCLUSIONS: Iprodione was fed to male and female Sprague-Dawley rats at dietary levels of 0, 150, 300, or 1,600 ppm (6.1, 12.4, 69.0 mg/kg/day in males and 8.4, 16.5, 95.0 mg/kg/day in females) for 2 years.

At 1,600 ppm (69.0 mg/kg/day) an increase was observed in benign interstitial cell tumors of the testes. No increase in the incidence of any type of tumor was observed in females under the conditions of this study.

LOEL (systemic) = 150 ppm (6.1 and 8.4 mg/kg/day for males and females, respectively) based on an increase in the incidence of fine vacuolation of the zona reticularis of the adrenal glands of low-dose males.

In addition, at 300 ppm (12.4 and 16.5 mg/kg/day for males and females, respectively) generalized enlargement of the cells of the zona glomerulosa in males and females and rarefaction and fine vacuolation of the zona fasciculata in the adrenal cortex were observed in males. Also, males showed interstitial cell hyperplasia in the testes, reduced spermatozoa in the epididymides, reduced secretion of the seminal vesicles, and an increased liver weight (after adjusting for body weight). Females showed increased hemosiderosis in the spleen. At the interim sacrifice at 53 weeks, males showed centrilobular hepatocellular enlargement.

At the highest dose tested, 1,600 ppm (69 and 95 mg/kg/day for males and females, respectively), decreases were observed in body weight gain (≈14-74%) and food consumption (≈5-8%) of males and females. At necropsy, males showed increases in testes (with epididymides) weights (after adjustment for body weight), testicular masses, small prostates, and small seminal vesicles with minimal contents. Histopathology revealed atrophy of the prostate and seminiferous tubule, prominent abnormal spermatogenic cells, and centrilobular hepatocellular enlargement in males. At the interim sacrifice at 53 weeks, both males and females showed generalized rarefaction and fine vacuolation of the zona fasciculata, males showed generalized enlargement of the cells of the zona glomerulosa and generalized fine vacuolation of the zona reticularis of the adrenal cortex, and females showed increased extramedullary hematopoiesis in the spleen.

CORE CLASSIFICATION: This study does not satisfy the guidelines for a combined chronic toxicity/oncogenicity test since no NOEL for systemic toxicity was established, and is therefore classified as Core Supplementary. The testing facility is requested to provide historical control data regarding the incidence of vacuolation of the zona reticularis. The study may be upgraded if review of the historical control data indicates that the incidence of the adrenal lesion in the low-dose males is not toxicologically significant.

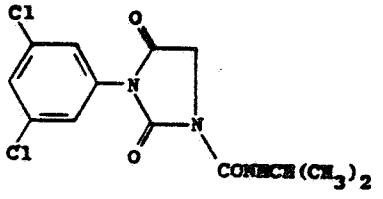
A. MATERIALS, METHODS, AND RESULTS

1. Test Article Description

Name: Iprodione

Composition: 3-(3,5-dichlorophenyl)-N-isopropyl-2,4-dioximidazolidine-1-carboxamide

Structure:



Batch number: DA 604

Purity: Determined by the Sponsor to be between 94.5% and 95.7%

Physical Property: Cream colored powder

Stability: Reported to be stable in the diet for at least 14 days

Storage Conditions: Stored at 4°C protected from light

2. Test Substance Analyses for Purity and Stability

Test diets were prepared weekly by first preparing a concentrated premix of the test substance in SDS Rat and Mouse No.1 maintenance diet. Final test diets were then obtained by mixing appropriate amounts of the premix with stock diet until the desired concentrations (150, 300, and 1,600 ppm) were achieved. Diets were stored at room temperature until use.

Chemical analyses for homogeneity and stability of the test material in the diet were not performed for this study. However, data were reported from a subchronic rat study (HRC Report No. RNP 320/90767) performed approximately 8 months prior to the start of this oncogenicity study. In the subchronic study, the same mixing procedure was used as that in the current study and homogeneity of diets containing 100 or 12,000 ppm of the test material was considered to have been acceptable (<10% difference between top, middle, and bottom of the mixture). Also, no loss of test material was observed following storage for 14 days in either an open feed jar or a closed polyethylene container.

Verification of the actual content of the test material in the diets in the current study was performed at study weeks 1, 2, 8, 16, 24, 32, 40, 48, 56, 64, 72, 80, 88, 96, and 104. Samples were analyzed using gas chromatography following extraction with either acetone or boiling acetonitrile. The acetone extraction method was used for samples from weeks 1-48 and the acetonitrile extraction method was used for samples from weeks 16-104. The acetone method gave variable results; therefore, the acetonitrile method was used to analyze most samples. Actual concentrations of test material in the diets were 121.9±19.7, 243.1±31.2, and 1,274.0±166.5 ppm using the acetone extraction method and 149.9±8.9, 287.5±14.4, and 1,546.8±92.5 ppm using the acetonitrile extraction method.

3. Animals

Sprague-Dawley rats [CRL:CD (SD) Br] (327 males and 333 females) were received from Charles River Laboratories, Portage, Michigan, and acclimated to laboratory conditions for approximately 2 weeks prior to the initiation of dosing. The rats were approximately 4 weeks of age at arrival. Upon arrival, animals were housed by sex (5/cage) and identified by leg tattoos and ear markings. During the pretest period, 5 rats/sex were sacrificed and tissues were examined microscopically to assess the health status of the shipment. Animals were selected for use in this study after elimination of those with

ophthalmological lesions and those judged by a veterinarian to be in poor health. The animals were then randomly assigned to the 4 treatment groups (60/sex/group plus an additional 10/sex/group for interim sacrifice at week 52) such that mean body weights of rats in each cage were approximately equal.

The rats were randomly assigned to the following control and test groups:

Dietary Levels (ppm)	Phase	Number of Animals Males	Number of Animals Females	Number of Weeks
0	Satellite Group	10	10	52
	Main Group	60	60	104
150	Satellite Group	10	10	52
	Main Group	60	60	104
300	Satellite Group	10	10	52
	Main Group	60	60	104
1,600	Satellite Group	10	10	52
	Main Group	60	60	104

The animal room was maintained at a temperature of 21±2°C, a relative humidity of 55±10%, and with a 12-hour light/dark cycle. Food (SDS Rat and Mouse No. 1 modified diet) and water (tap water) were provided *ad libitum* throughout the acclimation and study periods except when laboratory investigations were performed. In such cases, food was removed overnight prior to blood collection and water was removed overnight for urine collection.

Rationale for dose selection: The dose levels were selected based on the results of a 13-week dietary study in rats (HRC Report No. RNP 320/90767) with levels of 1,000, 2,000, 3,000, and 5,000 ppm. The 5,000-ppm group was reported to have been terminated after 8 weeks of treatment because of extreme toxicity (no further details were provided in this report). The 2,000- and 3,000-ppm groups showed decreased body weight, food intake, and microscopic changes (lesions not identified in this report). The 1,000-ppm group showed only a slight increase in liver weight. The 1,000-ppm group was considered to be a no-effect level.

4. Statistical Analyses

Food consumption (cumulative values), water consumption, body weight gain, hematology, clinical chemistry, and urinalysis data were analyzed by the following method: If 75% or more of the data for a particular parameter were equal to the mode, differences from the mode were analyzed using a Fischer's exact test followed by a Mantel's test. For other data, homogeneity of the variance was

determined using Bartlett's test, and data with homogeneous variances were analyzed using an analysis of variance. For data with heterogenous variance, a log transformation was attempted prior to analysis of variance. Following the analysis of variance, differences between treated groups and control groups were determined using a Student's t-test and Williams' test for trends. If the log transformation did not remove heterogeneity, data were analyzed using the Kruskal-Wallis test. A Shirley's test was used to determine between-group differences following the Kruskal-Wallis test.

Organ weight data were analyzed with an analysis of covariance, using body weight at the time of death as the covariate. Mortality was analyzed using a log-rank method. The incidence of nonneoplastic lesions was analyzed using the Fisher's exact test. Neoplastic lesions were analyzed using a Fischer's exact test, or in specific situations, by methods recommended by IARC that take tumor context into consideration (as described by Peto).

5. General Observations

(a) Mortality/moribundity/survival

Animals were observed for mortality/moribundity twice a day.

No treatment-related effects on survival were observed. The number of animals surviving to study termination was sufficient to assess oncogenicity. Percent survival at study termination ranged from 52% to 77% in males and from 44% to 58% in females. Both high-dose males and high-dose females showed greater survival than controls of the same sex.

(b) Clinical signs

Observations were made for adverse clinical signs at least once daily throughout the study. Additionally, detailed palpations were performed on individual rats once a week to monitor onset, severity, and location of each new palpable mass.

No treatment-related clinical signs and no increase in palpable masses were observed.

(c) Body weights/food and water consumption/test material intake

Body weights--Body weights were recorded at week -1 of the study, just prior to dosing, and weekly thereafter. Mean body weights were consistently decreased in high-dose males (average, 10%; range, 5-12%) and in high-dose females (average, 10%; range, 5-16%) when compared to controls.

Group mean cumulative body weight gains at selected intervals are summarized in Table 1. High-dose male rats showed statistically significantly decreased cumulative body weight gain between weeks 0 and 12, 12 and 22, and 0 and 104 of the study. The decreases in males at these intervals ranged from 13.7% to 16.4%. Body weight gains in high-dose males were essentially comparable to

controls after week 22. High-dose females showed statistically significant decreased body weight gain between weeks 0 and 12, 22 and 75, and 75 and 82. The decreases in females at these intervals ranged from 19.3% to 73.3%.

Food consumption--Food consumption (g/rat/cage) was recorded at week -1, just prior to dosing, and weekly thereafter.

Group mean cumulative food consumption values at selected intervals are presented in Table 2. Small (4.6-8.3%), but statistically significant, decreases in cumulative food consumption were observed in high-dose males during the intervals of weeks 1-12, 13-22, 23-104, and 1-104, and in high-dose females during the interval of weeks 13-22.

Feed efficiency--Food conversion ratios during the first 26 weeks of the study were calculated by dividing grams of food consumed by the gain in body weight.

High-dose males and females showed slightly increased (≈11-12%) food consumption per unit gain in body weight between weeks 1 and 26 when compared to controls. However, the report did not state whether the feed efficiency data were analyzed statistically or whether the increase was statistically significant.

Water consumption--Water consumption measurements were made during weeks 12, 25, and 51 on satellite animals only.

No statistically significant decreases in water consumption were observed.

Test material intake--Group mean test material intake (mg/kg/day) was calculated weekly using nominal dietary dose levels and weekly body weight and food consumption group mean values.

The average daily intake values of the test material for the low-, mid-, and high-dose groups were 6.1, 12.4, and 69.0 mg/kg/day, respectively, for males, and 8.4, 16.5, and 95.0 mg/kg/day, respectively, for females.

(d) Ophthalmoscopic examination

Ophthalmoscopic examinations were conducted on all animals prior to initiation of dosing, and during weeks 52 and 104 on animals in the control and high-dose groups only.

No treatment-related ocular changes were observed at week 52 or week 104.

6. Clinical Pathology

Blood samples were taken from 10 rats/sex/group from the satellite groups at weeks 26 and 52 and from 10 rats/sex/group from the main groups at weeks 78 and 104. The animals were fasted overnight prior to blood collection. All blood samples were drawn from the orbital

sinus of ether-anesthetized animals. The hematology and clinical chemistry parameters indicated by an "X" were analyzed:

(a) Hematology

X Packed cell volume*
X Hemoglobin (Hb)*
X Leukocyte count (WBC)*
X Erythrocyte count (RBC)*
X Platelet count*
X Thrombotest (TT)
X Leukocyte differential count
X Mean corpuscular Hb concentration (MCHC)
X Mean corpuscular volume (MCV)
X Red cell morphology

*Recommended by Subdivision F (November 1984) Guidelines

No treatment-related changes in any of the hematology parameters were observed. Statistically significant changes in a few parameters occurred, but these were not consistent over time and were not consistent between sexes.

(b) Blood (clinical) chemistry

Electrolytes

X Calcium*
X Chloride*
Magnesium
X Phosphorus*
X Potassium*
X Sodium*

Enzymes

X Alkaline phosphatase (ALP)
Cholinesterase
Creatinine phosphokinase*
Lactic acid dehydrogenase
X Serum alanine aminotransferase (SGPT)*
X Serum aspartate aminotransferase (SGOT)*
Gamma glutamyltransferase (GGT)

Other

X Albumin*
Albumin/globulin ratio
X Blood creatinine*
X Blood urea nitrogen*
X Cholesterol*
X Globulins
X Glucose*
X Total bilirubin*
Direct bilirubin
X Total protein*
Triglycerides

*Recommended by Subdivision F (November 1984) Guidelines

No treatment-related changes were observed in clinical chemistry parameters. Several parameters used to assess renal toxicity (blood urea nitrogen, creatinine, sodium, chloride, albumin, and total protein) showed statistically significant changes in treated rats relative to the controls. However, the changes were either very small (most statistically significant values were within control ranges at other time points in this study), failed to show a dose-response, were not consistent over time, or did not correspond with lesions observed during microscopic examination.

(c) Urinalysis

Samples for urinalysis were collected overnight from 10 male and 10 female rats at weeks 26 and 52 (satellite groups) and from 10 male and 10 female rats at weeks 78 and 104 (main groups). The animals were deprived of water during the collection period. The parameters indicated by an "X" below were examined:

Appearance*	Sediment (microscopic)	Bilirubin*
X Volume*	X Protein*	Blood
X Specific gravity*	X Glucose*	Nitrate
X pH*	X Ketones*	X Urobilinogen
	X Bile pigments	X Haem pigment

*Recommended by Subdivision F (November 1984) Guidelines

No treatment-related changes in any of the urinalysis parameters were observed.

7. Sacrifice and Pathology

All animals that died during the study, were sacrificed moribund, or were killed by carbon dioxide asphyxiation at week 52 (satellite group), or at study termination (104 weeks), were necropsied. Gross examination included verification of any palpable masses which were detected during the dosing period. Samples of those tissues and organs in the following list were taken from all animals and preserved in 10% neutral buffered formalin (except eyes which were saved in Davidson's fixative).

The tissues indicated by an "X" below were examined histologically in control, high-dose, and preterminal deaths. In addition, the lungs, livers, kidneys, and all tissues with gross lesions were examined in all animals. The tissues showing histopathological lesions in high-dose animals were also examined in rats at all doses. Tissues indicated by "XX" were also weighed.

Digestive System	Cardiovascular/Hematologic	Neurologic
X Tongue	X Aorta*	XX Brain*
X Salivary glands*	XX Heart*	X Peripheral nerve (sciatic nerve)*
X Esophagus*	X Bone marrow*	X Spinal cord (three levels)*
X Stomach*	X Lymph nodes*	XX Pituitary*
X Duodenum*	XX Spleen*	X Eyes (Optic nerve)*
X Jejunum*	X Thymus*	
X Ileum*		Glandular
X Cecum*	Urogenital	
X Colon*		XX Adrenals*
X Rectum*	XX Kidneys*	X Parathyroids*
XX Liver*	X Urinary bladder*	X Mammary gland*
X Pancreas*	XX Testes*	XX Thyroids*
	XX Epididymides	
Respiratory	X Prostate	Other
	X Seminal vesicle	
X Trachea*	XX Ovaries	X Bone (sternum and femur)*
X Lungs*	XX Uterus*	X Skeletal muscle*
	Vagina	X Skin*
		X All gross lesions and masses

*Recommended by Subdivision F (November 1984) Guidelines

(a) Organ weights and organ-to-body-weight ratios

Table 3 presents selected organ weight and organ-to-body-weight ratio data from rats at terminal sacrifice. Where organ weight data were adjusted for body weight, both adjusted and unadjusted data are presented. No treatment-related effects on organ weight were observed at the interim sacrifice. At study termination, a significant increase was observed in the absolute and relative (to body weight) weights of the livers of mid- and high-dose males. In addition, the high-dose males also showed increases in adjusted absolute and relative organ weights of the testes (with epididymides) and thyroid. The effects on thyroid and liver weights were observed only after the data had been adjusted for terminal body weight. The weight increase in the testes and epididymides was attributed by the study authors to the testicular tumors noted in the high-dose males at necropsy.

(b) Macroscopic pathology

Interim sacrifice

No treatment-related gross pathological changes were observed in rats sacrificed after 52 weeks of exposure.

Main study

The incidences of selected macroscopic findings for animals from the main study are presented in Table 4. Statistically significant increases were observed in the incidence of several lesions of the reproductive organs of high-dose males. These included testicular masses, small prostates, and small seminal vesicles with minimal contents. In addition, a statistically significant increase in the incidence of lung petechiae was observed in high-dose males.

The study authors also noted increases in the incidence of irregular cortical scarring in the kidneys of high-dose males and thickening of the uterus and lung petechiae of high-dose females. However, the incidence of these lesions did not achieve statistical significance ($p \leq 0.05$) when analyzed using the Fischer's exact test.

(c) Microscopic pathology

Interim sacrifice

Neoplastic lesions--There were no increases in the inoidences of neoplasms in treated groups versus controls after 52 weeks of treatment.

Nonneoplastic lesions--The incidences of selected nonneoplastic lesions noted at interim sacrifice are presented in Table 5. Statistically significant increases were observed in the incidences of several adrenal cortical lesions in high-dose rats. These included increases in generalized enlargement of cells of the zona glomerulosa and generalized fine vacuolation of the zona reticularis of high-dose males and generalized rarefaction and fine vacuolation of cells of the zona fasciculata in both high-dose males and females. Statistically significant increases were also observed in the incidence of centrilobular hepatocellular enlargement of mid- and high-dose males and high-dose females and in the incidence of extramedullary hematopoiesis of the spleen in the high-dose females.

The study authors also noted increases in the incidences of hemosiderosis in high-dose females and increases in focal enlargement of cells of the zona glomerulosa and generalized fine vacuolation of the cells of the zona fasciculata in high-dose males, but the incidence of these lesions did not achieve statistical significance ($p \leq 0.05$) when analyzed using the Fischer's exact test.

Main study

Neoplastic lesions--The incidences of both unilateral and bilateral benign interstitial cell tumors were statistically significantly increased in high-dose males. The percentage of high-dose males with either unilateral or bilateral interstitial cell tumors (48%) was outside the range from historical control

data from 7 previous studies (0-10%). In addition, the incidence of testicular tumors showed a statistically significant dose-related trend ($p<0.001$). Data in the following table were extracted from Study RNP 346/920808, Table 13b.

	Dietary level (ppm)			
Observations in testes	0	150	300	1,600
Unilateral interstitial cell tumor				
Termination	1/31	4/35	5/32	13/46**
Decedents	2/29	3/25	1/28	2/14
Combined	3/60	7/60	6/60	15/60**
Bilateral interstitial cell tumor				
Termination	0/31	0/35	1/32	12/46**
Decedents	0/29	0/25	0/28	2/14
Combined	0/60	0/60	1/60	14/60**

**Significantly different from control; $p \leq 0.01$.

Nonneoplastic lesions--Table 6 presents incidence data on selected treatment-related nonneoplastic findings for animals from the main study. The adrenal cortex and male reproductive organs showed the greatest prevalence of microscopic changes. Lesions observed in the adrenal cortex included focal enlargement of cells of the zona glomerulosa (mid- and high-dose males and females), generalized enlargement of cells of the zona glomerulosa (high-dose males), rarefaction and vacuolation of the zona fasciculata (mid- and high-dose males), and vacuolation of the zona reticularis (low-, mid-, and high-dose males). Lesions observed in the male reproductive tract included interstitial cell hyperplasia in the testes, reduced secretion in the seminal vesicles, and reduced spermatozoa in mid- and high-dose males and atrophy of the seminiferous tubules and prostate, and prominent abnormal spermatogenic cells in high-dose males.

Other nonneoplastic findings that were statistically significantly increased relative to controls included hemosiderosis of the spleen in mid- and high-dose females, prominent epithelial elements in the thymus in high-dose females, and centrilobular hepatocyte enlargement and sciatic nerve fiber degeneration in low- and high-dose males.

Findings that were significantly increased in animals that survived until study termination but that were not significant when combined with the incidence in decedents were vacuolation of the cells of the zona reticularis in low-dose males, interstitial cell hyperplasia of the testes in mid-dose males, reduced

spermatozoa in the epididymides in mid- and high-dose males, and basophilic/dilated cortical tubules with eosinophilic colloid in the kidneys in mid- and high-dose males, suggesting that these lesions required a longer time to onset at these doses.

The incidence of tubular hyperplasia in the ovaries appeared slightly increased in high-dose females at study termination (4/59 in controls versus 10/60 in high-dose females). However, a Fisher's Exact test showed that the increase was not statistically significant.

B. DISCUSSION

Review of the final report and supporting data indicates that the conduct and design of the study were adequate and the reporting of the results was, for the most part, accurate. Thyroid weights were incorrectly reported for males at all doses in the results section of the report, but this did not affect the overall interpretation of the study. The limitation of the study was that data regarding stability and homogeneity of the test material in the test diets were taken from a prior subchronic study in rats rather than being determined for the diets used in this study. This probably did not affect the study outcome since the mixing procedure was the same in both studies, but the absence of data from diets prepared in this study leaves a small amount of uncertainty regarding these parameters in the current study.

The doses used in this study resulted in both systemic toxicity and an increase in neoplasia. The male reproductive organs and the adrenal cortex were the primary target organs for iprodione. At the highest dose tested, the testes showed an increase in benign interstitial cell tumors and the incidences of these tumors at all doses showed a dose-related trend. Interstitial cell hyperplasia was increased in the testes of males at both the mid- and high-doses. Additional nonneoplastic lesions noted in the male reproductive tract included atrophy of the prostate and reduced secretion of the seminal vesicles in mid- and high-dose males, and atrophy of the seminiferous tubules of the testes, reduced spermatozoa, and abnormal spermatogenic cells in the epididymides of high-dose males.

Lesions of the adrenal cortex were observed in all 3 cell layers (zona glomerulosa, fasciculata, and reticularis), with males showing somewhat greater sensitivity than females. After only 1 year of exposure, rarefaction and vacuolation of cells of the zona fasciculata was observed in both high-dose males and females and enlargement of the cells of the zona glomerulosa and vacuolation of the cells of the zona reticularis were observed in high-dose males. After up to 2 years of exposure, increases in vacuolation of the zona reticularis (low-, mid-, and high-dose males), rarefaction and vacuolation of the zona fasciculata (mid- and high-dose males, and enlargement of the cells of the zona glomerulosa (mid- and high-dose males and females) were observed.

Other potential target organs of iprodione in treated rats include the liver and spleen. The weights of the livers of mid- and high-dose males were significantly elevated after 2 years of exposure, similar to effects seen in the subchronic rat study at 1,000 ppm. In addition, histopathological analyses showed increases in centrilobular

hepatocellular enlargement in mid- and high-dose males and high-dose females after 1 year of exposure and in high-dose males after up to 2 years of exposure. The spleens of females also showed histopathological changes after both 1 and 2 years of exposure. At the interim sacrifice, the spleens of high-dose females showed extramedullary hematopoiesis. After up to 2 years of exposure, both mid- and high-dose females showed hemosiderosis in the spleen.

Lesions in the kidneys, nerves, and thymus were observed only in high-dose animals and only to a limited degree, suggesting that these lesions may be of lesser toxicological importance than the lesions described above.

The LOEL for this study is 150 ppm based on the increase in vacuolation of the zona reticularis of the adrenal cortex of low-dose males. The choice of this lesion as a basis for the study LOEL is supported by the observation that the adrenal gland is a sensitive target for iprodione. The adrenal gland showed lesions at all three cell layers in high-dose males as early as one year into the study. With continued exposure, the lesions were observed at lower doses. In addition, the incidence of this lesion in the concurrent controls was relatively low, indicating that the lesion was also toxicologically significant.

In summary, an increase in benign interstitial cell tumors of the testes was observed in males at 1,600 ppm. The LOEL for systemic toxicity was 150 ppm based on a statistically significant increase in the incidence of vacuolation of the zona reticularis of the adrenal cortex of males. No NOEL for systemic toxicity was established in this study.

This study does not satisfy the guideline requirements for a combined chronic toxicity/oncogenicity study because no NOEL for toxicity was established. It is considered to be Core Supplementary. The testing facility is requested to provide historical control data for the incidence of vacuolation of the zona reticularis of the adrenal cortex in this strain of rats. The study may be upgraded pending review of the historical control data.

TABLE 1. Group Mean Body Weight Gains (g ± S.D.) of Rats Fed Diets Containing Iprodione for up to 104 Weeks[a,b,c]

Study Week	Mean Body Weight Gains (g ± S.D.) by Dietary Level (ppm)							
	0		150		300		1600	
	Male	Female	Male	Female	Male	Female	Male	Female
0-12	353 ±45	140 ±24	359 ±47	150 ±26	351 ±57	141 ±22	295** ±54 (83.6%)	113** ±22 (80.7%)
12-22	95 ±21	26 ±12	97 ±23	31 ±12	93 ±25	28 ±10	82** ±23 (86.3%)	24 ±9
22-75	190 ±76	168 ±58	205 ±77	181 ±66	191 ±72	159 ±66	182 ±65	135** ±54 (80.4%)
75-82	17 ±34	30 ±30	14 ±33	35 ±22	14 ±25	33 ±39	8 ±23	8** ±40 (26.7%)
82-104	7 ±86	16 ±65	10 ±66	27 ±53	-11 ±98	35 ±39	3 ±74	38 ±40
0-104	659 ±124	349 ±113	671 ±139	394 ±96	635 ±143	392 ±107	568** ±117 (86.2%)	322 ±90

[a]Data extracted from Study RNP 346/920808, p 33.
[b]Data include body weight gains of rats scheduled for interim sacrifice at week 53.
[c]Numbers in parentheses following significant findings indicate percentage of control.

**Significantly different from control value, $p \leq 0.01$.

TABLE 2. Group Mean Cumulative Food Consumption (g/rat ± S.D.) of Rats Fed Diets Containing Iprodione for up to 104 Weeks[a,b,c]

Study Week	Mean Cumulative Food Consumption (g/rat ± S.D.) by Dietary Level (ppm)							
	0		150		300		1600	
	Male	Female	Male	Female	Male	Female	Male	Female
1-12	2,454 ±88.5	1,745 ±93.9	2,506 ±106.6	1,803 ±79.8	2,469 ±127.9	1,736 ±90.7	2,250** ±145.6 (91.7%)	1,681 ±123.9
13-22	1,902 ±77.0	1,383 ±83.2	1,956 ±88.1	1,437 ±95.8	1,914 ±88.1	1,328 ±57.9	1,809** ±89.6 (95.1%)	1282** ±80.5 (92.7%)
23-104	15,784 ±479.4	12,351 ±627.2	15,951 ±670.7	13,088 ±649.6	15,712 ±588.4	12,504 ±907.7	15,053** ±664.8 (95.4%)	12,025 ±999.1
1-104	20,138 ±572.6	15,463 ±743.3	20,430 ±833.0	16,325 ±743.3	20,102 ±748.0	15,595 ±1002.9	19,170** ±800.9 (95.2%)	14,961 ±1125.5

[a]Data extracted from Study RNP 346/920808, p. 34.
[b]Data include food consumption data from rats scheduled for interim sacrifice at week 53.
[c]Numbers in parentheses following significant findings indicate percentage of control.

**Significantly different from control value, $p \leq 0.01$.

TABLE 3. Incidence of Selected Clinical Chemistry Parameters in Rats Fed Iprodione for up to 104 Weeks[a,b,c]

Parameter	Dose group (ppm)							
	0		150		300		1600	
	Male	Female	Male	Female	Male	Female	Male	Female
Urea Nitrogen (mg/dl)								
week 26	9	14	12*	13	11*	14	12*	15
week 52	11	14	12	11	12	13	11	14
week 78	11	11	10	13	10	13	11	13
week 104	11	10	12	12	12	11	10	12**
Albumin (g/dl)								
week 26	2.9	3.2	2.8	3.4	2.8	3.4	3.0	3.5*
week 52	3.0	3.5	2.9	3.5	2.9	3.6	3.0	3.6
week 78	2.7	3.2	2.6	3.3	2.7	3.3	2.6	3.4*
week 104	2.7	3.3	2.8	3.2	2.5	3.3	2.7	3.4
Total Protein (g/dl)								
week 26	6.7	6.9	7.2	7.2	6.9	7.2	6.8	7.3
week 52	7.1	7.8	7.2	7.8	7.2	8.0	7.3	7.9
week 78	6.7	7.2	6.7	7.5	6.7	7.4	6.6	7.7*
week 104	6.9	7.4	7.0	7.2	6.6	7.5	6.7	7.7
Creatinine (mg/dl)								
week 26	0.5	0.6	0.6	0.6	0.5	0.6	0.5	0.6
week 52	0.5	0.6	0.5	0.6	0.5	0.6	0.6	0.7*
week 78	0.5	0.5	0.5	0.6*	0.5	0.6*	0.5	0.6**
week 104	0.6	0.5	0.6	0.6	0.6	0.6*	0.6	0.6*

TABLE 3. Incidence of Selected Clinical Chemistry Parameters in Rats Fed Iprodione for up to 104 Weeks (continued)[a,b]

Parameter	Dose group (ppm)							
	0		150		300		1600	
	Male	Female	Male	Female	Male	Female	Male	Female
Sodium (mEq/l)								
week 26	142	141	142	141	141	143	141	141
week 52	142	141	141	140	141	143	142	141
week 78	140	140	141	138	141	139	142**	140
week 104	144	141	143	142*	143	142*	144	142*
Chloride (mEq/l)								
week 26	101	102	101	102	101	103	102	102
week 52	98	97	98	97	99	98	99	98
week 78	99	98	99	96	100	98	101**	98
week 104	102	97	101	99	101	100	103	99

[a]Data extracted from CBI, pp. 78-81, Table 8.
[b]N=60.
*Statistically significant at $p \leq 0.05$.
**Statistically significant at $p \leq 0.01$.

TABLE 4. Incidence of Selected Macroscopic Findings from Rats Fed Diets Containing Iprodione for up to 104 Weeks[a,b]

Organ/ Observation	Number of Animals with Lesion/Number of Animals Examined by Dietary Level (ppm)							
	0		150		300		1600	
	Male	Female	Male	Female	Male	Female	Male	Female
Testes - mass								
Termination	0/31	---	1/35	---	2/32	---	20/46##	---
Decedents	0/29	---	1/25	---	0/28	---	2/14	---
Combined	0/60	---	2/60	---	2/60	---	22/60##	---
Seminal vesicle - small/minimal contents								
Termination	1/31	---	0/35	---	3/32	---	7/46	---
Decedents	2/29	---	2/25	---	3/28	---	4/14	---
Combined	3/60	---	2/60	---	6/60	---	11/60#	---
Prostate - small								
Termination	0/31	---	1/35	---	1/32	---	3/46	---
Decedents	0/29	---	0/25	---	3/28	---	2/14	---
Combined	0/60	---	1/60	---	4/60	---	5/60#	---
Lung - petechiae								
Termination	7/31	6/26	8/35	5/28	7/32	7/30	14/46	13/35
Decedents	1/29	0/33	0/25	1/32	2/28	0/30	4/14#	0/25
Combined	8/60	6/59	8/60	6/60	9/60	7/60	18/60#	13/60

[a]Data extracted from Study RNP 346/920808, Tables 12a-12b.
[b]Dashes indicate finding not applicable.

#Significantly different from control, $p \leq 0.05$; data analyzed by reviewers using Fischer's exact test.
##Significantly different from control, $p \leq 0.01$; data analyzed by reviewers using Fischer's exact test.

TABLE 3. Selected Organ Weight and Organ-to-Body Weight Data from Rats Fed Diets Containing Iprodione for 104 Weeks[a,b]

Organ/Parameter	Organ Weights (g) and Organ-to-Body-Weight Ratios by Dietary level (ppm)							
	0		150		300		1600	
	Male	Female	Male	Female	Male	Female	Male	Female
Testes with epididymides[c]								
Organ weight (g)								
Unadjusted	4.06 ±0.93	---	3.74 ±0.63	---	3.83 ±0.79	---	4.76* ±1.50	---
Adjusted	ND		ND		ND		ND	
Organ:body weight	50 ±14	---	45 ±11	---	49 ±15	---	65## ±23	---
Thyroids[c]								
Organ weight (g)								
Unadjusted	37.9 ±6.6	31.7 ±9.9	40.4 ±12.3	33.2 ±6.7	41.1 ±14.7	31.8 ±7.3	40.8 ±12.9	29.1 ±6.7
Adjusted	36.2	32.0	37.1	32.4	39.0	31.4	41.3*	29.9
Organ:body weight	0.5 ±0.1	0.7 ±0.4	0.5 ±0.1	0.6 ±0.1	0.5 ±0.2	0.6 ±0.1	0.5 ±0.2##	0.6 ±0.1

TABLE 3 (continued). Selected Organ Weight and Organ-to-Body Weight Data from Rats Fed Diets Containing Iprodione for 104 Weeks[a,b]

Organ/Parameter	Organ Weight (g) and Organ-to-Body-Weight Ratios by Dietary Level (ppm)							
	0		150		300		1600	
	Male	Female	Male	Female	Male	Female	Male	Female
Liver								
Organ weight (g)								
Unadjusted	27.3 ±4.3	20.0 ±5.2	28.9 ±4.3	22.6 ±6.0	29.2 ±6.4	19.6 ±4.0	28.2 ±5.6	20.3 ±5.0
Adjusted	26.6	20.3	27.9	21.6	29.0*	18.8	29.6**	21.5
Organ:body weight	328 ±47	405 ±51	343 ±42	431 ±121	361## ±70	376 ±68	380## ±70	435 ±67

[a]Data extracted from Study RNP 346/920808, Tables 10 and 11 and Appendices 8 and 9.
[b]Mean ± S.D., except for adjusted data where S.D. was not given; dashes indicate finding not applicable.
[c]Data were log transformed prior to analysis of variance.

*Significantly different from control, $p<0.05$.
**Significantly different from control, $p<0.01$.

##Significantly different from control, $p<0.01$; data analyzed by reviewers using analysis of variance.

ND = not determined

TABLE 5. Incidence of Selected Non-Neoplastic Microscopic Findings from Rats Fed Diets Containing Iprodione for up to 52 Weeks - Interim Sacrifice[a]

Organ/ Observation	Number of Animals with Lesion/Number of Animals Examined by Dietary Level (ppm)							
	0		150		300		1600	
	Male	Female	Male	Female	Male	Female	Male	Female
Adrenals								
Generalized enlargement of cells of zona glomerulosa	0/10	0/10	0/10	0/10	0/10	0/10	8/10##	3/10
Generalized rarefaction and fine vacuolation of zona fasciculata	0/10	0/10	0/10	0/10	0/10	1/10	5/10#	8/10##
Generalized fine vacuolation of zona reticularis	0/10	0/10	0/10	0/10	0/10	0/10	5/10#	0/10
Liver								
centrilobular hepatocyte enlargement	0/10	0/10	0/10	0/10	4/10#	1/10	5/10#	4/10#
Spleen								
Extramedullary hemopoiesis	0/10	3/10	0/1	0/10	0/0	2/10	2/10	9/10##

[a]Data extracted from Study RNP 346/920808, Table 13a.

#Significantly different from control, $p \leq 0.05$; data analyzed by reviewers using Fischer's exact test.
##Significantly different from control, $p \leq 0.01$; data analyzed by reviewers using Fischer's exact test.

TABLE 6. Incidence of Selected Nonneoplastic Microscopic Findings in Rats Fed Diets Containing Iprodione for up to 104 Weeks[a,b]

Organ/ Observation	Number of Animals with Lesion/Number of Animals Examined by Dietary Level (ppm)							
	0		150		300		1600	
	Male	Female	Male	Female	Male	Female	Male	Female
Adrenals								
Focal enlargement of cells of zona glomerulosa								
Termination	1/31	0/26	2/35	0/28	6/32	3/30	14/46**	2/35
Decedents	0/29	0/33	4/25	1/32	3/28	2/30	3/14#	4/25*
Combined	1/60	0/59	6/60	1/60	9/60##	5/60#	17/60##	6/60#
Generalized enlargement of cells of zona glomerulosa								
Termination	0/31	0/26	0/35	0/28	1/32	0/30	6/46*	1/35
Decedents	0/29	0/33	0/25	0/32	1/28	0/30	7/14**	2/25
Combined	0/60	0/59	0/60	0/60	2/60	0/60	13/60##	3/60
Generalized rarefaction and fine vacuolation of zona fasciculata								
Termination	0/31	0/26	1/35	0/28	3/32	0/30	23/46**	2/35
Decedents	1/29	1/33	4/25	0/32	5/28	1/30	5/14*	3/25
Combined	1/60	1/59	5/60	0/60	8/60#	1/60	28/60##	5/60
Generalized fine vacuolation of zona reticularis								
Termination	1/31	0/26	8/35*	1/28	15/32**	0/30	12/46**	2/35
Decedents	6/29	0/33	6/25	0/32	9/28	1/30	8/14*	1/25
Combined	7/60	0/59	14/60	1/60	24/60##	1/60	20/60##	3/60

TABLE 6 (continued). Incidence of Selected Non-Neoplastic Microscopic Findings in Rats Fed Diets Containing Iprodione for up to 104 Weeks[a,b]

Organ/ Observation	Number of Animals with Lesion/Number of Animals Examined by Dietary Level (ppm)							
	0		150		300		1600	
	Male	Female	Male	Female	Male	Female	Male	Female
Testes								
Interstitial cell hyperplasia								
Termination	5/31	---	7/35	---	12/32**	---	28/46**	---
Decedents	2/29	---	6/25	---	1/28	---	7/14**	---
Combined	7/60	---	13/60	---	13/60	---	35/60##	---
Atrophy of seminiferous tubules								
Termination	5/31	---	9/35	---	10/32	---	22/46**	---
Decedents	5/29	---	5/25	---	4/28	---	2/14	---
Combined	10/60	---	14/60	---	14/60	---	24/60##	---
Epididymides								
Reduced spermatozoa								
Termination	0/31	---	3/35	---	5/32*	---	6/46*	---
Decedents	2/29	---	0/25	---	2/28	---	0/14	---
Combined	2/60	---	3/60	---	7/60	---	6/60	---
Prominent abnormal spermatogenic cells								
Termination	0/31	---	0/35	---	2/32	---	5/46	---
Decedents	0/29	---	0/25	---	0/28	---	0/14	---
Combined	0/60	---	0/60	---	2/60	---	5/60#	---
Prostate - Atrophy								
Termination	1/31	---	2/35	---	5/32	---	13/46**	---
Decedents	1/29	---	0/25	---	2/28	---	0/14	---
Combined	2/60	---	2/60	---	7/60	---	13/60##	---

TABLE 6 (continued). Incidence of Selected Non-Neoplastic Microscopic Findings in Rats Fed Diets Containing Iprodione for up to 104 Weeks[a,b]

Organ/ Observation	Number of Animals with Lesion/Number of Animals Examined by Dietary Level (ppm)							
	0		150		300		1600	
	Male	Female	Male	Female	Male	Female	Male	Female
Seminal vesicles - Reduced secretion								
Termination	0/31	---	1/35	---	7/32**	---	10/46**	---
Decedents	4/29	---	3/25	---	5/28	---	2/14	---
Combined	4/60	---	4/60	---	12/60##	---	12/60##	---
Sciatic - Nerve fiber degeneration								
Termination	27/31	8/26	35/35	8/28	30/32	10/29	39/46	19/35
Decedents	3/29	3/33	8/25	3/32	4/28	1/30	4/14	2/25
Combined	30/60	11/59	43/60#	11/60	34/60	11/59	43/60#	21/60
Thymus - Prominent epithelial elements								
Termination	NR	1/24	NR	0/1	NR	0/1	NR	7/35
Decedents	NR	0/33	NR	1/32	NR	0/29	NR	1/25
Combined	NR	1/57	NR	1/33	NR	0/30	NR	8/60#
Spleen - Hemosiderosis								
Termination	1/31	9/26	1/15	11/28	0/12	20/30*	1/46	22/35**
Decedents	4/29	13/33	5/25	14/32	4/28	15/29	2/14	15/25
Combined	5/60	22/59	6/40	25/60	4/40	35/59#	3/60	37/60##
Liver - Centrilobular hepatocyte enlargement								
Terminal	0/31	0/26	0/35	0/28	0/32	0/30	3/46	0/35
Decedents	0/29	0/33	0/25	0/32	0/28	0/30	3/14*	1/25
Combined	0/60	0/59	0/60	0/60	0/60	0/60	6/60#	1/60

TABLE 6 (continued). Incidence of Selected Non-Neoplastic Microscopic Findings in Rats Fed Diets Containing Iprodione for up to 104 Weeks[a,b]

Organ/ Observation	Number of Animals with Lesion/Number of Animals Examined by Dietary Level (ppm)							
	0		150		300		1600	
	Male	Female	Male	Female	Male	Female	Male	Female
Kidneys - Basophilic dilated cortical tubules with eosinophilic colloid								
Termination	5/31	12/26	11/35	8/28	15/32**	8/29	19/46**	8/35
Decedents	4/29	2/33	4/25	4/32	4/28	4/30	0/14	3/25
Combined	9/60	14/59	15/60	12/60	19/60	12/59	19/60	11/60

[a]Data extracted from Study RNP 346/920808, Table 13d.
[b]Dashes indicate finding not applicable.

*Significantly different from control, $p<0.05$
**Significantly different from control, $p<0.01$

#Significantly different from control, $p<0.05$; data analyzed by reviewers using Fischer's exact test.
##Significantly different from control, $p<0.01$; data analyzed by reviewers using Fischer's exact test.

NR = Not reported.

IPRODIONE TOX REVIEW 010570

Page_____ is not included in this copy.

Pages 30 through 49 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

X___ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.